IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PFIZER INC., Plaintiff, v. TEVA PHARMACEUTICALS USA and TEVA PHARMACEUTICAL INDUSTRIES LTD. Defendants.	Civil Action No. 06-89 (GMS)

DECLARATION OF CYNTHIA LAMBERT HARDMAN, ESQ. IN SUPPORT OF THE MOTION OF DEFENDANTS TEVA PHARMACEUTICALS USA, INC. AND TEVA PHARMACEUTICAL INDUSTRIES LTD. TO TRANSFER VENUE TO THE SOUTHERN DISTRICT OF NEW YORK PURSUANT TO 28 U.S.C. § 1404(A)

I, Cynthia Lambert Hardman, Esq., hereby declare as follows:

1. I am an attorney-at-law of the state of New York and an associate of the law firm of Kenyon & Kenyon LLP, counsel, together with Morris, James, Hitchens & Williams LLP, for defendants Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Ltd. ("Teva Ltd.") (collectively, "Teva") in this action. I make this Declaration in support of Teva's Motion to Transfer Venue to the Southern District of New York Pursuant to 28 U.S.C. § 1404(a).

2. Kenyon & Kenyon LLP is counsel to Teva USA in *Teva Pharmaceuticals USA, Inc. v. Pfizer Inc.*, 03cv7423 and 04cv4979 (LAP) (consolidated), which is pending in the United States District Court for the Southern District of New York (the "New York Action"). A true and correct copy of the complaints in that action, which were filed on September 22, 2003 and June 24, 2004, respectively, are attached hereto as Exhibits A and B. The New York Action is assigned to Judge Loretta A. Preska.

3. In the New York Action, Pfizer Inc. ("Pfizer") moved to dismiss the complaints for lack of subject matter jurisdiction. Pfizer subsequently brought counterclaims against Teva USA for infringement of U.S. Patent Nos. 5,605,889 (the "'889 patent") and 6,268,489 (the "'489 patent"). Attached hereto as Exhibits C and D, respectively, are true and correct copies of Pfizer's Answers in case nos. 03cv7423 and 04cv4979.

4. Before substantial discovery had taken place in the New York Action, Pfizer granted Teva USA a covenant not to sue with respect to the '889 patent. The terms of the covenant have not been made public. Attached hereto as Exhibit E is a true and correct copy of a submission to the United States Patent and Trademark Office ("PTO") during reissue proceedings for the '889 patent, in which Pfizer disclosed the covenant to the PTO.

5. On June 20, 2005, Teva USA filed a Consolidated Amended Complaint in the New York Action. Pfizer's Answer to that complaint, which it filed on July 15, 2005, included a counterclaim against Teva USA for infringement of the '489 patent. Teva USA's Consolidated Amended Complaint and Pfizer's Answer were filed under seal pursuant to the Protective Order issued in that action, and therefore copies of these documents are not attached.

6. On September 23, 2005, the parties in the New York Action filed summary judgment motions. In support of their summary judgment motions, Teva USA and Pfizer submitted declarations from ten experts, including experts in polymorphism, x-ray crystallography, organic chemistry, drug formulation, solid-state nuclear magnetic resonance spectroscopy, and infrared and Raman spectroscopy. These declarations were all filed under seal, and their contents are subject to the Protective Order in the New York Action. The topics covered in the declarations include, among other things, the compound azithromycin and its crystalline forms; the crystalline form of the API used in Teva's azithromycin products; the

research, development, composition, formulation, manufacture, testing and labeling of Teva's azithromycin products; the analytical techniques used to identify and quantify crystalline forms in general, and crystalline forms of azithromycin in particular, including x-ray crystallography, infrared and Raman spectroscopy and solid state nuclear magnetic resonance spectroscopy; and the scientific theories that attempt to explain when and why particular crystalline forms of compounds, including azithromycin, may be found in particular samples.

7. In late January 2006, counsel for Pfizer informed counsel for Teva USA that Pfizer had concluded that Teva's azithromycin tablets do not contain azithromycin dihydrate. Pfizer subsequently granted Teva USA a covenant not to sue with respect to the '489 patent. The terms of the covenant have not been made public.

8. In view of Pfizer's covenant on the '489 patent, Judge Preska denied as moot the parties' motions for summary judgment, but gave Teva USA permission to make an attorney's fees motion. Attached hereto as Exhibit F is a true and correct copy of Judge Preska's February 17, 2006 Order.

9. On February 14, 2006, Teva filed a declaratory judgment action against Pfizer in the Southern District of New York, *Teva Pharmaceuticals USA, Inc. and Teva Pharmaceutical Industries Ltd. v. Pfizer Inc.*, 06cv1134. Attached hereto as Exhibit G is a true and correct copy of the Complaint in that case.

10. Attached hereto as Exhibit H is a true and correct copy of a printout from Pfizer's website, www.pfizer.com, which includes a list titled "Pfizer Locations."

11. Attached hereto as Exhibit I are true and correct copies of submissions made by Pfizer to the PTO during the prosecution of U.S. Patent No. 6,977,243.

12. According to Pfizer's submissions to the PTO, the inventors listed on the '243 patent reside in Quaker Hill, Connecticut and Stonington, Connecticut. Quaker Hill and Stonington are approximately 125 and 135 miles, respectively, from the Southern District of New York, and approximately 254 and 264 miles, respectively, from the District of Delaware.

I declare under penalty of perjury that the foregoing is true and correct to the best of my knowledge and belief.

Cynthia Lambert Hardman

Executed on Feb. 22, 2006.

CERTIFICATE OF SERVICE

I hereby certify that on the 23rd day of February, 2006, I electronically filed the foregoing document, **DECLARATION OF CYNTHIA LAMBERT HARDMAN, ESQ. IN SUPPORT OF THE MOTION OF DEFENDANTS TEVA PHARMACEUTICALS USA, INC. AND TEVA PHARMACEUTICAL INDUSTRIES LTD. TO TRANSFER VENUE TO THE SOUTHERN DISTRICT OF NEW YORK PURSUANT TO 28 U.S.C. § 1404 (a)**, with the Clerk of the Court using CM/ECF which will send notification of such filing to the following:

Rudolf E. Hutz, Esq.
Daniel C. Mulveny, Esq.
Connolly Bove Lodge & Hutz LLP
1007 North Orange Street
Wilmington, DE 19801

Additionally, I hereby certify that on the 23rd day of February, 2006, the foregoing document was served as indicated:

VIA HAND DELIVERY
Rudolf E. Hutz, Esq.
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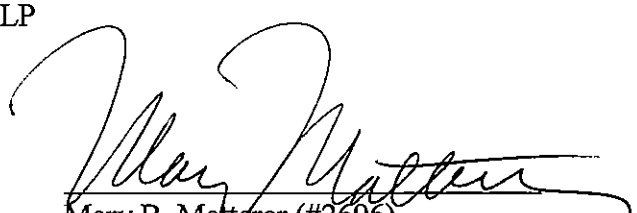

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EXHIBIT A

IN THE UNITED STATES DISTRICT COURT FOR THE
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC.,

Plaintiff,

v.

PFIZER INC.,

Defendant.

Civil Action No.

03 CV 7427

JUDGE BAER

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), for its Complaint against Pfizer Inc. ("Pfizer"), alleges as follows:

THE PARTIES

1. Teva is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090. Teva is a developer, manufacturer, and marketer of generic pharmaceutical products in the United States.

2. On information and belief, Pfizer is a Delaware corporation with its principal place of business at 235 East 42nd Street, New York, New York, 10017-5575.

3. On information and belief, Pfizer owns U.S. Patent No. 5,605,889 ("the '889 patent"), entitled "Method of Administering Azithromycin," a copy of which is attached hereto as Exhibit A.

4. On information and belief, Pfizer owns U.S. Patent No. 6,268,489 ("the '489 patent"), entitled "Azithromycin Dihydrate," a copy of which is attached hereto as Exhibit B.

5. On information and belief, Pfizer holds New Drug Application ("NDA") No. 50-711 for ZITHROMAX® 250 mg azithromycin dihydrate ("azithromycin") tablets, and NDA No. 50-730 for ZITHROMAX® 600 mg azithromycin tablets.

JURISDICTION AND VENUE

6. This Court has original jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), in that it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 *et seq.*

7. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction seeking a declaratory judgment that the '889 and '489 patents are invalid and not infringed.

8. Personal jurisdiction exists over the defendant because defendant has its principal place of business within this district, and because defendant does business within this district.

9. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and 1400(b).

THE PRESENCE OF AN ACTUAL CONTROVERSY

10. ZITHROMAX® is an oral antibiotic. In its 2002 Annual Report, Pfizer states that in 2002, sales of ZITHROMAX® totaled $1.5 billion.

11. Teva holds Abbreviated New Drug Application ("ANDA") Numbers 65-153, filed December 12, 2002, and 65-150, filed November 27, 2002. These ANDAs are directed to a generic version of ZITHROMAX® and have been accepted by the U.S. Food and Drug Administration ("FDA") for review. By preparing and filing these ANDAs, Teva has made

substantial preparation to make, use, import, offer to sell, and sell a generic version of ZITHROMAX® in the U.S.

12. On information and belief, Pfizer's '889 and '489 patents contain claims directed to azithromycin, a component of ZITHROMAX®, and Pfizer would therefore assert the '889 and '489 patents against Teva for alleged infringement of those patents if Teva commercially marketed generic versions of ZITHROMAX® tablets.

13. Pfizer has demonstrated a willingness and intention to enforce foreign patents that are related to ZITHROMAX®. Pfizer brought suit in Canada against Novopharm, an affiliate of Teva, asserting the Canadian equivalent to the '489 patent. *Pfizer Canada and Pfizer Inc. v. Novopharm*, Federal Court – Trial Division, Ontario, Court File No. T-74-03.

14. Pfizer has refused to grant Teva a covenant that it will not enforce the '889 and '489 patents against Teva. On August 5, 2003, Teva hand delivered to Pfizer a letter requesting such a covenant. Teva requested that Pfizer respond to the letter within forty five days of receipt. To date, Teva has received no response from Pfizer. Teva's August 5, 2003 letter to Pfizer is attached hereto as Exhibit C.

15. Pfizer (or its predecessor) has also demonstrated its intention to protect other products from generic competition by Teva. On at least five occasions, Pfizer sued or maintained suit against Teva (or its related entities) for patent infringement relating to other drugs for which Teva has filed an ANDA: (i) *Pfizer Inc. and Pfizer Technologies Ltd. v. Novopharm Ltd.*, 00-cv-01475 (N.D. Ill.), concerning fluconazole; (ii) *Pfizer Inc./Warner-Lambert v. Teva*, 00-cv-4589 and 00-cv-4168 (D.N.J.), concerning gabapentin; (iii) *Schwarz Pharma, Inc., Schwarz Pharma AG and Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.*, 01-cv-4995 (D.N.J.), concerning moexipril; (iv) *Bayer and Pfizer v. Biovail & Teva*, 01-cv-

1205 and 01-cv-1206 (D.P.R.), concerning nifedipine; and (v) *Warner-Lambert v. Teva USA*, 99-cv-0922 (D.N.J.), concerning quinipril.

16. Based upon Pfizer's refusal to covenant to not enforce the '889 and '489 patents against Teva, Pfizer's suit against Teva's affiliate to enforce the Canadian equivalent of the '489 patent, and Pfizer's pattern of aggressively enforcing its patents to attempt to prevent generic competition by Teva, Teva is under a reasonable apprehension that Pfizer will sue Teva, alleging infringement of the '889 and '489 patents.

17. To avoid legal uncertainty and to protect its substantial investment (and anticipated future investments) in its manufacturing process for its generic ZITHROMAX® product, Teva has instituted this declaratory judgment action.

COUNT I
DECLARATORY JUDGMENT OF NONINFRINGEMENT

18. Teva's manufacture, use, offer for sale, sale, or importation of an FDA-approved generic version of ZITHROMAX® does not, and would not, infringe any properly construed claim of the '889 patent.

COUNT II
DECLARATORY JUDGMENT OF NONINFRINGEMENT

19. Teva's manufacture, use, offer for sale, sale, or importation of an FDA-approved generic version of ZITHROMAX® does not, and would not, infringe any properly construed claim of the '489 patent.

COUNT III
DECLARATORY JUDGMENT OF PATENT INVALIDITY

20. The claims of the '889 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

COUNT IV
DECLARATORY JUDGMENT OF PATENT INVALIDITY

21. The claims of the '489 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

PRAYER FOR RELIEF

WHEREFORE, Teva respectfully requests the Court enter judgment against Pfizer to include:

A. A declaration that Teva's manufacture, use or sale of Teva's generic version of ZITHROMAX® will not infringe United States Patent No. 5,605,889;

B. A declaration that Teva's manufacture, use or sale of Teva's generic version of ZITHROMAX® will not infringe United States Patent No. 6,268,489;

C. A declaration that United States Patent No. 5,605,889 is invalid;

D. A declaration that United States Patent No. 6,268,489 is invalid;

E. An award of Teva's reasonable costs and attorneys' fees in connection with this action; and

F. All such other and further relief as the Court may deem just and proper.

Respectfully submitted,
KENYON & KENYON

Dated: 9/22/03

By: _____

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EXHIBIT A

US005605889A

United States Patent [19]

Curatolo et al.

[11] Patent Number: 5,605,889

[45] Date of Patent: Feb. 25, 1997

[54] **METHOD OF ADMINISTERING AZITHROMYCIN**

[75] Inventors: William J. Curatolo, Niantic; George H. Foulds, Waterford, both of Conn.; Hylar L. Friedman, Brattleboro, Vt.

[73] Assignee: Pfizer Inc., New York, N.Y.

[21] Appl. No.: 235,069

[22] Filed: Apr. 29, 1994

[51] Int. Cl.[6] A61K 31/70; A61K 9/14; A61K 9/20

[52] U.S. Cl. 514/29; 514/960; 424/464; 424/465; 424/474; 424/480; 424/481; 536/7.2

[58] Field of Search 514/29, 960; 536/7.2; 424/464, 465, 474, 480, 481

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,382,085	5/1983	Scivoliso et al.	514/29
4,474,768	10/1984	Bright	514/29
4,517,359	5/1985	Kobrehel et al.	536/7.4
4,963,531	10/1990	Remington	514/29
5,250,518	10/1993	Kobrehel et al.	514/29
5,350,839	9/1994	Asaka et al.	536/7.4

FOREIGN PATENT DOCUMENTS

0307128	3/1989	European Pat. Off. .
0582396	2/1994	European Pat. Off. .

OTHER PUBLICATIONS

Curatolo et al. *J. Pharm. Sci.*, vol. 77 (4), pp. 322–324, (1988).

Welling et al. *J. Pharm. Sci.*, vol. 67 (6), pp. 764–766, (1978).

Welling et al. *J. Pharm. Sci.*, vol. 68 (2), pp. 150–155, (1979).

Malmborg, A. *Curr. Med. Res. Opin.* vol. 5 (Suppl. 2), pp. 15–18, (1978).

Drew et al., Pharmacotherapy, 12, 3, 161–173 (1992).

Chu et al., J. Clin. Pharmacol., 32, 32–36 (1992).

Hopkins, S., Am. J. Med., 91 (Suppl 3A), 40S–45S (1991).

Toothaker et al., Ann. Rev. Pharmacol. Toxicol. vol. 20, 173–199, 1980.

Russell et al., Pharmaceutical Research, vol. 10, No. 2, 187–196, 1993.

CA Abstracts: vol. 120:38194a; 1994.

Zithromax (Trademark of Pfizer, Inc.) Capsules Package Insert for azithromycin capsule dosage form sold commercially in U.S.

Primary Examiner—John Kight
Assistant Examiner—Howard C. Lee
Attorney, Agent, or Firm—Peter C. Richardson; Gregg C. Benson; James T. Jones

[57] **ABSTRACT**

An oral dosage form of azithromycin which does not exhibit an adverse food effect; Specific azithromycin oral dosage forms including tablets, powders for oral suspensions and unit dose packets; Methods of treating microbial infections with the dosage forms; And therapeutic packages containing the dosage forms.

99 Claims, No Drawings

METHOD OF ADMINISTERING AZITHROMYCIN

This invention relates to a dosage form of azithromycin, and also to a method of treating a microbial infection which involves administering azithromycin in the fed state to a mammal, including a human patient, in need of such treatment.

BACKGROUND OF THE INVENTION

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly useful as antibiotics.

In general, it is known that the absorption and bioavailability of any particular therapeutic agent can be affected by numerous factors when dosed orally. Such factors include the presence of food in the gastrointestinal (GI) tract because, in general, the gastric residence time of a drug is usually significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug is affected beyond a certain point due to the presence of food in the GI tract, the drug is said to exhibit a "food effect". Food effects are important inasmuch as, when a drug exhibits an adverse food effect, there is risk associated with administering it to a patient who has eaten recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remediate the condition for which the drug was administered.

Other factors can also be involved in drug bioavailability, the following being a non-comprehensive listing:

(1) The particular dosage form can affect bioavailability. For example, the gastric residence time of a tablet or capsule can be significantly longer than that of a suspension, and the difference may vary depending on whether the subject has eaten or is fasted.

(2) The pH of the stomach varies, between the fed and fasted state, with the amount of food therein, and drugs which are decomposition-sensitive to pH can be affected accordingly.

(3) The capacity of the liver to metabolize an absorbed drug (so-called "first pass" metabolism) may vary with the type of meal eaten. For example some vegetables (such as brussels sprouts) can stimulate first pass metabolism of some drugs, but not others. Grapefruit juice, on the other hand, may inhibit first pass metabolism of some drugs.

(4) Bile, which is released from the gallbladder into the small intestine when a meal is ingested, has the ability to solubilize poorly soluble drugs and thus increase bioavailability.

Additional factors can also be involved in the absorption and bioavailability of a particular drug, and absorption can actually be increased as well as decreased. These additional factors include, for example, pH-dependent solubility, site-specific intestinal permeation rate, instability to intestinal enzymes, susceptibility to first pass metabolism, and instability to colonic bacteria. Given the plethora of factors which can influence bioavailability, there usually is no way to predict, in the absence of actual testing, whether a particular drug will exhibit a food effect. For example, Toothaker and Welling, *Ann. Rev. Pharmacol. Toxicol.*, 1980, 173–99, discuss various drugs whose absorption is delayed in the presence of food (cephalexin, cefaclor, metronidazole, aspirin, diclofenac, indoprofen, digoxin, cimetidine), whose absorption may be unaffected by food (ampicillin, erythromycin estolate, spiramycin, propylthiouracil, oxazepam, bendroflumethiazide), and whose absorption is increased in the presence of food (erythromycin ethylsuccinate, nitrofurantoin, 8-methoxsalen, propranolol, metoprolol, dicoumarol, diazepam, hydrochlorothiazide).

As a further example, there appears to be no clear or definitive support for the proposition that tablets might exhibit fewer food effects than capsules, or vice-versa. Toothaker and Welling review studies which demonstrate food related reduced absorption for tablet dosage forms of erythromycin stearate, aspirin, nafcillin, and sotalol.

In the case of azithromycin, at least one (unpublished) study has shown that the absorption of azithromycin can be adversely affected if the patient is in a fed state, and it has heretofore been conventional wisdom that azithromycin capsule dosage forms exhibit a so-called adverse "food effect". Accordingly, in countries where azithromycin is currently available for use in the treatment of human patients, the product is sold with the specific direction that it be administered only in the fasted state, i.e. at least one hour before or two hours following a meal.

It would accordingly be useful if azithromycin could be administered to patients that have eaten recently and also if a dosage form for azithromycin were available which could be administered to patients that have eaten, as well as patients in a fasted state.

SUMMARY OF THE INVENTION

This invention provides an oral dosage form of azithromycin which can be administered to a mammal (including humans) that has eaten and which exhibits substantially no adverse food effect, excluding any dosage form which contains a significant amount of an alkaline earth oxide or hydroxide. The dosage form exhibits a mean $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, the terms "$(AUC_{fed})/(AUC_{fst})$" and "90% confidence limit" being fully defined below.

In a further aspect, this invention provides a specific oral azithromycin dosage form which does not exhibit an adverse food effect. The dosage form comprises azithromycin and a pharmaceutically acceptable carrier, as hereinafter further detailed and described. The dosage form is in the form of a tablet (including both swallowable-only and chewable forms), in the form of a unit dose packet (sometimes referred to in the art as a "sachet"), in the form of a suspension made from a unit dose packet, in the form of a powder for oral suspension, and in the form of an oral suspension per se. It is noted that when a unit dose packet is constituted, it is probably mainly in the form of a suspension if reconstituted according to directions, although the extent of suspension versus solution depends on a number of factors such as pH. The use of the term "suspension" herein is intended to embrace liquids containing azithromycin partially in suspension and partially in solution, and also totally in solution.

In a further aspect, this invention provides a method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an oral dosage form which exhibits substantially no adverse food effect. The dosage form employed exhibits a

mean $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

Reference herein and in the claims to a mammal (including humans) that has "eaten" means that the mammal has eaten food of any sort within one hour prior to dosing up to two hours after dosing.

In a further aspect, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithromycin which does not exhibit an adverse food effect contained therein, and, associated with said container, written matter non-limited as to whether the dosage form can be taken with or without food.

It is noted that powders for oral suspension and unit dose packets, of course, are not ingested directly by patients; rather, they are reconstituted in a suitable vehicle. These terms are nonetheless considered to be within the penumbra of the term "dosage form" for purposes of this invention.

Capsules as a dosage form do not form a part of the invention.

For purposes of this invention azithromycin may be administered alone or in combination with other therapeutic agents.

A food effect can be detected and quantified as described, for example in Toothaker and Welling, supra, by determining the area under a curve (AUC) which plots the serum concentration (e.g., in μg/mL) of azithromycin along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the values for AUC represent a number of values taken from all the subjects in a patient test population and are, therefore, mean values averaged over the entire test population. By measuring the area under the curve for a fed population of subjects (AUC_{fed}) and comparing it with the area for the same population of fasted subjects (AUC_{fst}), it can be determined whether a given drug exhibits an adverse food effect or not.

For definitional purposes of this invention, and specifically with respect to azithromycin dosage forms only, a dosage form of azithromycin exhibits an adverse food effect if, after dosing a population, once fasted and once fed, the mean $(AUC_{fed})/(AUC_{fst})$ is below the value 0.80 and/or the lower 90% confidence limit for this ratio is below 0.75.

Conversely, a dosage form of azithromycin which does not exhibit an adverse food effect is one which, when tested on a test population, exhibits a value for $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 and a lower 90% confidence limit for this value of at least 0.75. The value for mean $(AUC_{fed})/(AUC_{fst})$ can have any value above 0.80 and still be within the scope of this invention, though it is preferred that it have an upper (mean) limit of 1.25, with an upper 90% confidence limit of 1.40 or below.

A population of "fed" subjects, for purposes of definition and for measuring AUC_{fed}, is one made up of subjects each of whom has eaten a Food and Drug Administration (FDA)-recommended standard high fat breakfast within a period of twenty minutes, and then ingested (i.e., swallowed) the test dosage form essentially immediately thereafter. A standard high-fat breakfast consists of, for example, two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk. This standard high-fat breakfast contains approximately 964 calories, 54% supplied as fat (58 gm) and 12% supplied as protein, calculated using the monograph "Nutritive Value of Foods", U.S. Department of Agriculture Home and Garden Bulletin Number 72. Additional food can also be consumed within the twenty minute period and the subject still qualifies as "fed". A "fasted subject" for purposes of definition and for measuring AUC_{fst} is one who has not eaten for at least eight hours, typically overnight, prior to ingestion of the dosage form.

The 90% confidence limits on AUC_{fed}/AUC_{fst} for a particular population, in this case either a fed or a fasted population, can be (and were) calculated as described following using Schairman's two one-sided test procedure.

The log-transformed AUCs were analyzed by means of an analysis of variance appropriate for a two-period, two-treatment crossover design. Analysis was carried out using Statistical Analysis System (SAS) software from SAS Institute, Cary, N.C. SAS procedure referred to in the SAS software as PROC GLM was used to determine sequence, subject within sequence, period and treatment (Fed/Fasted) effects. The sequence effect was tested using the [subject within sequence] mean square from the analysis of variance (ANOVA) as an error term. All other effects were tested against residual error (error mean square) from the ANOVA. The LSMEANS statement of SAS was used to calculate the least square means and their standard errors and covariances. These were used to obtain estimates for adjusted differences between treatment means and standard errors associated with these differences (log transformed).

The 90% confidence interval for two-way crossover design was constructed, based on these estimates, as the difference plus (or minus) the standard error of the difference times the 95th percentile of the t-distribution with (twice the sample size-2) degrees of freedom. The anti-log was taken on the limits to obtain the corresponding confidence for the ratio.

That a dosage form according to the invention does not exhibit an adverse food effect is surprising in view of the fact that azithromycin is unstable at low (acid) pH, on the order of the acidity encountered at the pH of stomach acid. The inventors have demonstrated that azithromycin breaks down if exposed to stomach juices which inherently exhibit acid pH. Thus, without being bound to any mechanism of action, it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention.

Commonly assigned co-pending application Ser. No. 07/922,262 filed Jul. 30, 1992 discloses taste masking compositions of bitter pharmaceutical agents, such as azalide antibiotics, containing, as a taste-masking component, a basic compound selected from the group consisting of alkaline earth oxides and alkaline earth hydroxides. A composition of this invention, if it contains an alkaline earth oxide or hydroxide at all, contains less than a taste-masking amount of the taste-masking component. A composition of this invention therefore preferably contains less than about 1% of an alkaline earth oxide or hydroxide, and may be free of such taste-masking component entirely.

DETAILED DESCRIPTION

Azithromycin is typically present in formulations according to the invention in an amount of from about 25 mg to about three grams, preferably 250 mg to two grams, for treatment of a human. If dosage forms are to be used for animal/veterinary applications, the amount can, of course, be adjusted to be outside these limits depending, for example, on the size of the animal subject being treated (e.g., a horse). The term "azithromycin" includes the pharmaceutically acceptable salts thereof, and also anhydrous as well as hydrated forms. The azithromycin is preferably present as the dihydrate, disclosed, for example, in published European Patent Application 0 298 650 A2.

In order to test whether a particular azithromycin dosage form exhibits an adverse food effect, the most reliable method is actually to test the dosage form in vivo on a subject population, once fed and once fasted, determine the level of serum (or plasma) azithromycin with time, plot curves for the concentration of serum (or plasma) azithro-

mycin with time in each subject (fed and fasted) as described above, determine the area under each curve (conventionally, for example by simple integration) and finally determine whether the mean ratio (AUC_{0-96})/(AUC_{∞}) exceeds 0.80, and whether the lower 90% confidence limit equals or exceeds 0.75.

It is believed that the azithromycin dosage forms of the invention do not exhibit a food effect in large part because they either provide azithromycin ready for dissolution in the GI tract essentially immediately following ingestion (suspensions), or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution. While not wishing to be bound by theory, it is believed that if an azithromycin dosage form provides azithromycin immediately following ingestion for dissolution in the GI tract, or at least provides azithromycin for dissolution within a certain time period following ingestion, the azithromycin will be absorbed into the bloodstream at a rate which results in substantially no adverse food effect. In order for an adequate rate of absorption to occur, it is believed that the dosage form should provide azithromycin at a rate such that at least about 90% of the azithromycin dissolves within about 30 minutes following ingestion, preferably within about 15 minutes following ingestion. A non-capsule dosage form comprising azithromycin is also considered to fall within the scope of the appended claims if it satisfies the in vitro dissolution testing requirements enumerated herein. An azithromycin dosage form according to the invention exhibits at least about 90% dissolution of azithromycin within about 30 minutes, preferably within 15 minutes, when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml approx. 0.1M dibasic sodium phosphate buffer, pH 6.0, 37° C. with paddles turning at 100 rpm. This test is described in US Pharmacopeca XXII, pp. 1578–1579. Dosage forms which pass this test under more stringent conditions (lower volume of buffer, greater amount of dosage form, lower temperature, higher pH, lower paddle speed) are also included under the above definition. Any modifications to this test are also described herein. The time required for dissolution of a particular azithromycin dosage form in this in vitro test is believed to be an indicator of the time required for dissolution of the dosage form in the GI environment. The following discussion is believed pertinent in this regard.

It is generally assumed and observed that the in vitro dissolution rate of dosage forms exhibits a rank order correlation with in vivo dissolution, particularly for a single dosage form type, e.g. tablets, which vary systematically in composition. Thus in vitro dissolution evaluation serves an important role in control of the quality of manufactured dosage forms. It is not necessarily true that the in vitro dissolution rate is exactly the same as the in vivo dissolution rate. This is not surprising, since the artificial conditions of an in vitro dissolution test (e.g. vessel geometry, stirring rate, stirring method, and so forth) are not identical to the conditions under which a dosage form disintegrates and dissolves in the GI tract.

When comparing dosage forms of different type, e.g. capsules and tablets, in vitro dissolution rate should correlate roughly with in vivo dissolution rate. However, subtle differences exist between the disintegration mechanisms of capsules and tablets. For capsules, at least partial dissolution of the gelatin shell must precede complete dissolution of the enclosed drug. Furthermore, capsule shells generally dissolve first at the capsule ends, and later at the capsule center. Tablets, on the other hand, disintegrate homogeneously. Thus subtle differences may exist in the in vitro/in vivo dissolution correlation when comparing capsules and tablets. For example, capsules and tablets which exhibit similar in vitro dissolution rates may exhibit subtle differences in in vivo dissolution rate. While such subtle differences may have no therapeutically significant effect on systemic bioavailability of an orally dosed drug, there are situations in which a significant effect may occur. For example, if a drug has the potential to exhibit an adverse food effect, drug-containing capsules and tablets which exhibit similar in vitro dissolution rates may actually differ with respect to whether an adverse food effect is observed when the dosage forms are orally dosed. In fact, this has been observed for azithromycin, as exemplified in the Examples herein.

For the in vitro dissolution studies disclosed herein, azithromycin was assayed by HPLC, utilizing a 5 micron alumina based hydrocarbonaceous spherical particle chromatographic column (15 cmx0.4 cm), and a 5 micron alumina based hydrocarbonaceous spherical particle precolumn (5 cmx0.4 cm) (both available from ES Industries, Marlton, N.J.). A mobile phase consisting of 71% phosphate buffer/29% acetonitrile (pH 11) was used, with electrochemical detection (e.g. Bioanalytical Systems, West Lafayette, Ind., LC-4B amperometric detector with dual series glassy carbon electrodes).

For in vivo food effect studies, serum azithromycin is assayed using an HPLC assay described by R. M. Shepard et al. (1991) J. Chromatog. Biomed. Appl. 565, 321–337, with amperometric electochemical detection. Alternatively, any assay method that produces equivalent results, for example, bioassay, can be used.

Tablets according to the invention contain, as necessary ingredients, azithromycin and a disintegrant. Examples of tablet disintegrants are starch, pregelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, crosslinked sodium carboxymethylcellulose (sodium croscarmellose; crosslinked starch available under the registered trademark Ac-Di-Sol from FMC Corp., Philadelphia, Pa.), clays (e.g. magnesium aluminum silicate), microcrystalline cellulose (of the type available under the registered trademark Avicel from FMC Corp. or the registered trademark Emcocel from Mendell Corp., Carmel, N.Y.), alginates, gums, surfactants, effervescent mixtures, hydrous aluminum silicate, cross-linked polyvinylpyrrolidone (available commercially under the registered trademark PVP-XL from International Specialty Products, Inc.), and others as known in the art. Preferred disintegrants for azithromycin tablets are sodium croscarmellose (Ac-Di-Sol), sodium starch glycolate (available commercially under the registered trademarks Primojel from Avebe (Union, N.J.) or Generichem, (Little Falls, N.J.) and Explotab from Mendell Corp.), microcrystalline cellulose (Avicel), and cross-linked polyvinylpyrrolidone (PVP-XL). Azithromycin tablets of this invention comprise azithromycin and 1–25% disintegrant, preferably 3–15% disintegrant based on total tablet weight. For example, a 463.5 mg tablet (250 mg activity azithromycin) may contain 9 mg sodium croscarmellose and 27 mg pregelatinized starch.

In addition to the active ingredient azithromycin and a disintegrant, tablets according to this invention may be formulated to optionally include a variety of conventional excipients, depending on the exact formulation, such as binders, flavorings, buffers, diluents, colors, lubricants, sweetening agents, thickening agents, and glidants. Some excipients can serve multiple functions, for example as both binder and disintegrant.

Examples of binders are acacia, cellulose derivatives (such as methylcellulose and carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose), gelatin, glucose, dextrose, xylitol, polymethacrylates, polyvinylpyrrolidone, starch paste, sucrose, sorbitol, pregelatinized starch, gum tragacanth,

alginic acids and salts thereof such as sodium alginate, magnesium aluminum silicate, polyethylene glycol, guar gum, bentonites, and the like. A preferred binder for azithromycin tablets is pregelatinized starch (available, for example, under the registered trademark Starch 1500, from Colorcon, Inc., West Point, Pa.).

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants leaves, flowers, fruits, and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, and cassia oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot, and so forth. The amount of flavoring may depend on a number of factors including the organoleptic effect desired. Generally the flavoring will be present in an amount of from 0.5 to about 3.0 percent by weight based on the total tablet weight, when a flavor is used.

A variety of materials may be used as fillers or diluents. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. starch 1500), cellulose (e.g. microcrystalline cellulose; Avicel), dihydrated or anhydrous dibasic calcium phosphate (available commercially under the registered trademark Emcompress from Mendell or A-Tab and Di-Tab from Rhone-Poulenc, Inc., Monmouth Junction, N.J.), calcium carbonate, calcium sulfate, and others as known in the art.

Lubricants can also be employed herein in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants are magnesium stearate, stearic acid, glycerylbehaptate, polyethylene glycol, ethylene oxide polymers (for example, available under the registered trademark Carbowax from Union Carbide, Inc., Danbury, Conn.), sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, and others as known in the art. Preferred lubricants are magnesium stearate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants generally comprise 0.5 to 7.0% of the total tablet weight.

Other excipients such as glidants and coloring agents may also be added to azithromycin tablets. Coloring agents may include titanium dioxide and/or dyes suitable for food such as those known as F. D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, annato, carmine, turmeric, paprika, and so forth. A coloring agent is an optional ingredient in the compositions of this invention, but when used will generally be present in an amount up to about 3.5 percent based on the total tablet weight.

As known in the art, tablet blends may be dry-granulated or wet granulated before tableting. Alternatively, tablet blends may be directly compressed. The choice of processing approach depends upon the properties of the drug and chosen excipients, for example particle size, blending compatibility, density and flowability. For azithromycin tablets, granulation is preferred, with wet granulation being most preferred. Azithromycin may be wet-granulated, and then other excipients may be added extragranularly. Alternatively, azithromycin and one or more excipients may be wet-granulated. In addition, tablets may also be coated, with a coating that exhibits little or no effect on or interference with tablet dissolution, to assure ease of swallowing or to provide an elegant appearance.

In a preferred embodiment, tablets of this invention are film-coated to provide ease of swallowing and an elegant appearance. Many polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropylmethylcellulose (HPMC). HPMC may be obtained commercially, for example from Colorcon Corp., in coating formulations containing excipients which serve as coating aids, under the registered trademark Opadry. Opadry formulations may contain lactose, polydextrose, triacetin, polyethyleneglycol, polysorbate 80, titanium dioxide, and one or more dyes or lakes. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylate-methacrylate copolymers.

The tableting process itself is otherwise standard and readily practiced by forming a tablet from a desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press. Tablet formulation and conventional processing techniques have been widely described, for Example in *Pharmaceutical Dosage Forms: Tablets;* Edited By Lieberman, Lachman, and Schwartz; Published by Marcel Dekker, Inc., 2d Edition, Copyright 1989, the text of which is herein incorporated by reference.

The azithromycin dosage forms of this invention also include powders to make oral suspensions, and also the oral suspensions themselves. Generally the powder is a non-caking, free flowing powder which is sold direct to pharmacies or other retail outlets and then made up into the actual suspension by a pharmacist. The oral suspension is thus the actual dosage form ingested by patients. The typical shelf life for a suspension is about five days because azithromycin therapy is generally of five days duration.

Azithromycin suspensions according to the invention contain, as necessary ingredients in addition to azithromycin, one or more thickening agents in a total amount of 0.1 to 2%, and a buffer or pH-altering agent in an amount of 0.1 to 2.5%, with percentages being based on the weight of the dry powder formulation. Dispersing agents may also be used in an amount of from 0.05 to 2%. Preservatives may also be used in an amount from 0.1 to 2%.

Suitable thickening agents function as suspending agents and include, for example, hydrocolloid gums known for such purpose, examples of which include xanthan gum, guar gum, locust bean gum, gum tragacanth, and the like. Alternatively, synthetic suspending agents may be used such as sodium carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like.

Dispersing agents include colloidal silicon dioxide, available from Cabot Corporation, Boston, Mass. under the trade designation Cab-O-Sil.

For the purpose of preparing formulations of a powder for oral suspension, the bitter taste of azithromycin may be masked by including a basic buffer or pH-altering agent which will provide a pH of approximately 10 in the constituted suspension. Maintenance of the pH at around 10 minimizes the quantity of azithromycin in solution, and thus masks the bitter taste of the drug. Many combinations of flavors or flavor systems may be used in addition to mask the bitter taste of azithromycin. Preferred flavors are those which provide a constant flavor for approximately 5 days at the elevated pH of the formulation after constitution. A preferred flavor system consists of spray dried cherry #11929, artificial creme de vanilla #11489, and spray-dried artificial banana #15223 available commercially from Bush Boake Allen, Inc., Chicago, Ill. Artificial sweeteners may also be used.

A powder used to make a suspension herein may also contain conventional optional ingredients such as (1) wetting agents such as sorbitan monolaurate, polysorbate 80, and sodium lauryl sulfate; (2) anti-foaming agents and (3) sweeteners and fillers such as glucose. The powder may also contain a buffer to maintain a high pH upon reconstitution, as discussed above. Suitable buffers and pH-altering agents

include anhydrous tribasic sodium phosphate, anhydrous sodium carbonate, glycine, and the like. Suitable preservatives are well known, for example sodium benzoate and the like. After swallowing, azithromycin from a suspension dissolves quickly.

In the preparation of azithromycin powder for oral suspension formulations, all ingredients may be blended together and deagglomerated, as known in the art. Preferably, azithromycin and flavors are blended, and other ingredients are separately blended. Finally, these two blends are blended and deagglomerated.

Preferred oral suspensions are those which resuspend easily after constitution with aqueous media and which do not cake on storage after constitution. Preferred suspensions contain sucrose NF, when sucrose is used, and anhydrous excipients when available, to assure facile suspension upon constitution. The drug-containing powder is generally reconstituted with water.

Suspensions of this invention exhibit about 90% dissolution of azithromycin in vitro in about 15 minutes. The test can be summarized as follows:

Shake the azithromycin-containing bottle to loosen the powder, and constitute the sample as per label instructions, e.g. as described in Example 12 to provide a 40 mg/ml azithromycin suspension. Shake the bottle vigorously for 2 minutes, then allow the bottle to sit for 30 minutes. Shake again vigorously for 15 seconds. Withdraw 5 ml from the bottle (typically equivalent to 200 mg of azithromycin), taking care to eliminate air bubbles. Carefully dispense the 5 ml aliquot of the azithromycin suspension approximately 10 cm over the surface of the dissolution medium (0.10M sodium phosphate buffer, pH 6.0) in a USP Apparatus 2, with the paddles positioned 2.5 cm from the bottom of the vessels. Begin rotating the paddles at 25 rpm, after the Oral Suspension samples have sunk to the bottom of the vessels. Remove approximately 10 ml from the dissolution vessel at each sampling time, filter, and assay filtrate for azithromycin using the HPLC assay described previously.

An azithromycin unit dose packet dosage form (also referred to herein as a "sachet") consists of a unit packet, designed to be emptied into an aqueous vehicle, for example water or a natural or artificial fruit beverage. The packet contains a blend of azithromycin and excipients which is thus reconstituted. The packet contains, as necessary ingredients, azithromycin and a dispersing agent which makes the sachet powder free flowing, for example colloidal silicon dioxide such as Cab-O-Sil from Cabot. Generally the dispersing agent is present in an amount of about 0.2 to 2.0% by weight based on the weight of the dry sachet as it is to be sold. The dispersing agent also serves as a glidant. The formulation may also optionally contain ingredients including (1) a filler or sweetener (e.g. glucose); (2) a buffer (e.g. sodium phosphate); (3) a wetting agent such as a surfactant, for example sodium lauryl sulfate, and (4) flavors such as any of those enumerated herein, and the like. The powder in the packet flows freely and disperses quickly, essentially immediately upon stirring when reconstituted. Azithromycin unit dose packet dosage forms may be prepared by blending and deagglomerating all ingredients, as known in the art. Preferably, the filler (e.g. sucrose), buffer (e.g. anhydrous tribasic sodium phosphate), and glidant (e.g. colloidal silicon dioxide) are blended and deagglomerated, followed by blending with azithromycin and flavors, followed by deagglomeration. The azithromycin in the packet dissolves quickly when evaluated as follows. The contents of a packet are added to a 250 ml beaker containing 60 ml water treated with the Milli-Q Plus system, Millipore Corp. (>18 megohms resistivity). The contents of the beaker are stirred with a spoon until a homogeneous suspension is obtained (1–2 min.). With the paddles raised, the suspension is poured into the center of a dissolution vessel of a USP-2 dissolution apparatus containing 900 ml 0.1M sodium phosphate buffer, pH 6.0. The paddles are then lowered into the vessel, and rotation is begun at 50 rpm. 10 mL aliquots are removed at each time point, filtered, and filtrates are assayed for azithromycin in solution, using an HPLC assay as described above. Using this method, greater than 90% dissolution of a 1 gm azithromycin packet is observed in less than 5 minutes. The packet thus does not exhibit an adverse food effect.

As stated, the oral azithromycin dosage forms disclosed and described above can be administered to a mammal, including man, in need of such treatment when the mammal has eaten, regardless of how recently and of the nature and quantity of food, without exhibiting an adverse food effect. To this end, and as an additional feature of the invention, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithromycin which does not exhibit an adverse food effect contained therein, and, associated with said package, written (i.e., printed) matter non-limited as to whether the dosage form can be taken with or without food. The written matter is of the type containing information and/or instructions for the physician, pharmacist or patient. The written material can be "non-limited as to whether the dosage form can be taken with or without food" by virtue of including no statement regarding whether or not the dosage form can be taken with or without food, i.e. the statement is silent with regard to food effects. Alternatively, the written material can be non-limited by containing one or more statements affirmatively informing the user (i.e., the patient, pharmacist, or physician) that the said oral dosage form can be taken by or administered to a patient regardless of whether the patient has eaten or otherwise imbibed food (optionally, for example, also stating something like "without regard to type or quantity of food"). The written material can not contain limiting language with respect to food, e.g. "This dosage form can not be taken with food" or "This dosage form may only be given after the patient has fasted" or the like.

The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual dosages for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

Printed or otherwise written matter is associated with the package in which the azithromycin dosage form is sold. The term "associated with" is intended to include all manners in which written matter, such as instructional or informational materials can be associated with a medicament, as known conventionally in the art. Thus written matter can be associated with the container, for example, by being: written on a label (e.g., the prescription label or a separate label) adhesively affixed to a bottle containing an azithromycin suspension; included inside a container as a written package insert, such as inside a box which contains unit dose packets; applied directly to the container such as being printed on the wall of a box; or attached as by being tied or taped, for example as an instructional card affixed to the neck of a bottle via a string, cord or other line, lanyard or tether type device. The written matter may be printed directly on a unit dose pack or blister pack or blister card. If the written matter affirmatively contains a non-limiting statement, the written

matter may contain other information in addition. An affirmative non-limiting statement may, for example, read like the following exemplary statement:

> This product does not exhibit an adverse food effect and may accordingly be administered to patients whether or not they have eaten and without regard to type or quantity of food.

or something similar, such as "may be taken without regard to food".

The invention will now be illustrated by the following examples which are not to be taken as limiting. In general, the examples demonstrate that (1) azithromycin capsules exhibit an adverse food effect, and that more slowly dissolving capsules exhibit a larger food effect, and (2) azithromycin fast dissolving tablet, powder for oral suspension, and unit dose packet dosage forms do not exhibit an adverse food effect.

EXAMPLE 1

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a capsule dosage form with moderate dissolution rate.

Capsules were prepared which contained 250 mg activity azithromycin. The formula for these capsules is presented in Table I. The dissolution behavior of these capsules was evaluated by the method previously discussed, using rotating paddles, 100 rpm, 900 ml pH 6.0 phosphate buffer at 37 degrees C. The average % azithromycin dissolved at 15 minutes was 25%, and at 30 minutes was 76%.

The effect of feeding on azithromycin bioavailability was determined as follows. Eleven healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast (food and fluid) of 12 hr. The dose was swallowed with 150 ml water, and a further 150 ml water was taken at 1 hr post-dosing. On the other occasion, the subjects consumed a meal consisting of milk, bread and butter, bacon, 2 fried eggs, and coffee. The dose was administered with 150 ml water within 30 minutes of completion of the meal. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition. The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.22, with lower and upper 90% confidence levels of 0.06 and 0.84, respectively.

TABLE I

Formulation of 250 mg Azithromycin Capsules. Prepared in #0 white opaque locking type capsules.

INGREDIENT	MG/CAPSULE
Azithromycin*	263.72
Lactose, anhydrous	149.88
Corn starch, hydrous	47.0
Magnesium stearate/Sodium lauryl sulfate (90/10)	9.40
TOTAL	470.0

*Based on a bulk potency of 94.8%; Non-stoichiometric hydrate.

EXAMPLE 2

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a capsule dosage form which dissolved more quickly than the capsules of Example 1.

Azithromycin capsules (250 mg strength) were prepared according to the formula in Table II. Dissolution of azithromycin from these capsules was evaluated as in Example 1. In 15 minutes, 97% of the encapsulated azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from this dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after consumption of a meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two ounces of ham, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces whole-fat milk. The oral doses were administered with 250 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on azithromycin oral bioavailability. The average AUCfed/AUCfasted was 0.80, with lower and upper 90% confidence levels of 0.67 and 0.96, respectively.

TABLE II

Formula for Azithromycin capsules. This formula was prepared as a dry granulation and was loaded into #0 opaque locking capsules.

INGREDIENT	MG/CAPSULE
Azithromycin Dihydrate*	262.05
Lactose, anhydrous	151.55
Corn starch, hydrous	47.00
Magnesium stearate/Sodium lauryl sulfate	9.40
TOTAL	470.00

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.

EXAMPLE 3

This example is comparative and demonstrates the effect of a light breakfast on systemic exposure of azithromycin dosed in a capsule dosage form which dissolves quickly.

Azithromycin capsules (250 mg strength) were prepared according to the formula in Table II. Dissolution of azithromycin from these capsules was evaluated as in Example 1. In 15 minutes, 99% of the encapsulated azithromycin was dissolved.

The effect of a light (Continental) breakfast on azithromycin bioavailability from this dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 1000 mg azithromycin (4×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed after consumption of a light breakfast consisting of two rolls with butter and jam and Ca. 300 ml of coffee or tea with milk. The oral doses were administered with 240 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 46.5 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the

area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.71, with lower and upper 90% confidence levels of 0.53 and 0.95, respectively.

EXAMPLE 4

This example demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a tablet dosage form which dissolves quickly.

Azithromycin tablets were prepared according to the formula given in Table III. Dissolution evaluation was carried out as in Example 1. At 30 minutes, 100% of the azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from these tablets was determined as follows. Twelve healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg tablets), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after consumption of a meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two teaspoons of butter and two pats of jelly, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes, ingested over a twenty minute period. The oral doses were administered with 240 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.97, with lower and upper 90% confidence levels of 0.82 and 1.13, respectively.

TABLE III

Formula for azithromycin film coated tablets. This formula was compressed to form a 0.262" × 0.531" modified capsule, upper engraved "Pfizer", lower scored, tablet, and was coated with "pink Opadry".

INGREDIENT	WEIGHT (MG/UNIT)
Azithromycin dihydrate*	262.05
Pregelatinized starch**	27.00
Calcium phosphate dibasic, anhydrous	138.84
Sodium croscarmellose***	9.00
Magnesium stearate/Sodium lauryl sulfate (50/10)	13.11
Pink Opadry II##	18.00

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.
**Starch 1500.
***Ac-Di-Sol.
##Contains lactose, hydroxypropyl methylcellulose, titanium dioxide, triacetin, and D&C Red No. 30 Aluminum Lake.

EXAMPLE 5

This example demonstrates the effect of a Japanese meal on systemic exposure of azithromycin dosed in a tablet dosage form which dissolves quickly.

A tablet dosage form of azithromycin was prepared according to the formula described in Table IV. Dissolution of this dosage form was evaluated as in Example 1. In 15 minutes, 100% of the azithromycin dose was dissolved.

The effect of feeding on azithromycin bioavailability from these tablets was determined as follows. Eight healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg tablets), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed 30 minutes after consumption of a Japanese meal consisting of rice, miso soup, fried egg, seaweed, spinach, and pickles. The oral doses were administered with 200 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.00, with lower and upper 90% confidence levels of 0.87 and 1.15, respectively.

TABLE IV

Azithromycin film-coated tablet formula. Capsular plain white film-coated tablets (0.262" × 0.531") were compressed and then coated with "White Opadry" and "Clear Opadry".

INGREDIENT	WEIGHT (MG/TABLET)
Azithromycin dihydrate*	262.05
Pregelatinized starch**	27.00
Calcium phosphate dibasic, Anhydrous	138.84
Sodium croscarmellose***	9.00
White Opadry##	12.825
Clear Opadry###	0.675
Magnesium Stearate/ Sodium Lauryl Sulfate (50/10)	13.11

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.
**Starch 1500.
***Ac-Di-Sol.
##Contains hydroxypropyl methylcellulose, titanium dioxide, polyethyleneglycol, and polysorbate 80.
###Contains hydroxypropyl methylcellulose and polyethyleneglycol.

EXAMPLE 6

This example compares the effects of a high fat breakfast and a low fat breakfast on systemic exposure of azithromycin dosed in a "Powder for Oral Suspension" dosage form.

An azithromycin "Powder for Oral Suspension" was prepared according to the formula in Table V. This formula was designed to wet and disperse quickly when reconstituted with an aqueous vehicle. Dissolution of this suspension was evaluated as described in the "Detailed Description". In 15 minutes 97% of the azithromycin dose dissolved; in 30 minutes 99.6% of the azithromycin dose dissolved.

The effect of a high fat meal and a low fat meal on azithromycin bioavailability from this suspension dosage form was determined as follows. Six healthy male human volunteers were orally dosed with 500 mg azithromycin (12.5 ml of a 40 mg/ml oral suspension), on each of 3 occasions. On one occasion, the subjects were dosed after an overnight fast of 10–12 hr. On another occasion the subjects were dosed after consumption of a high fat meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two pats of butter, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes, ingested over a twenty minute period. On the third occasion, the subjects were dosed after consumption of a low fat meal consisting of one ounce of Cheerios (registered trademark of

General Mills Inc.) cereal and eight ounces of whole milk. The oral doses were administered with 240 ml water (two 60 ml rinses of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. For the high fat meal, the average AUCfed/AUCfasted was 1.01, with lower and upper 90% confidence levels of 0.79 and 1.28, respectively. For the low fat meal, the average AUCfed/AUCfasted was 1.04, with lower and upper 90% confidence levels of 0.82 and 1.33, respectively.

TABLE V

Formula for azithromycin "Powder for Oral Suspension". To reconstitute this formulation, 0.52 ml water was added per gm dry formulation.

INGREDIENT	WEIGHT (MG/BOTTLE)
Azithromycin dihydrate*	838.57
Sucrose	15487.74
Sodium phosphate tribasic, anhydrous	70.01
Hydroxypropylcellulose (Klucel-EF)	26.62
Xanthan gum (Kelzol)	26.62
FD&C Red #40	0.67
Spray Dried Cherry #11929	59.94
Art. Cream de Vanilla #11489	133.28
S.D. Art. Banana #15223	99.96
TOTAL	16743.41

*Based on a bulk potency of 95.4%.

EXAMPLE 7

This example demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a "Single Dose Packet" (sachet) dosage form.

A "Single Dose Packet" (sachet) dosage form of azithromycin was prepared according to the formula described in Table VI. Dissolution of this dosage form was evaluated as described in the "Detailed Description" above. In 15 minutes, 99% of the azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from this sachet dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 1000 mg azithromycin (1 gm sachet), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast of at least 12 hr, and on the other occasion the subjects were dosed after consumption of a high-fat meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two teaspoons of butter and with two pats of jelly, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes. The oral doses were administered with 240 ml water (two 60 ml rinses of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96, and 120 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.12, with lower and upper 90% confidence levels of 0.99 and 1.27.

TABLE VI

Formula for azithromycin "Unit Dose Packet" dosage form. This blend was prepared, and filled into 3.25" x 4" white paper/aluminum/polyethylene laminate sachets. To reconstitute for dosing, the contents of a sachet is added to 60 ml water, and stirred well.

INGREDIENT	WEIGHT (GM/UNIT)
Azithromycin dihydrate*	1.048
Sucrose	9.707
Sodium phosphate tribasic, anhydrous	0.088
Colloidal silicon dioxide	0.053
Spray Dried art. cherry #11929	0.038
Spray Dried art. banana #15223	0.064
TOTAL	11.000

*Equivalent to 1 gm azithromycin, based on a bulk potency of 95.4% for azithromycin dihydrate.

EXAMPLE 8

Azithromycin tablets of this invention were prepared at 150, 200, 250, 300, 500, and 600 mg dosage strengths. Tablet cores were prepared by wet granulation of all tablet core ingredients (except magnesium stearate/sodium lauryl sulfate). The dried granules were blended with the lubricant mixture magnesium stearate/sodium lauryl sulfate, followed by tableting on a tablet press. Tablets were coated with an aqueous film coat comprising colored and/or clear Opadry. These tablet formulations do not exhibit an adverse food effect. Tablet formulations were as described in Table VII.

TABLE VII

Examples of azithromycin tablet formulations which do not exhibit a food effect.

	WEIGHT (MG/TABLET)					
Component	150 MG STRENGTH	200 MG STRENGTH	250 MG STRENGTH	300 MG STRENGTH	500 MG STRENGTH	600 MG STRENGTH
Azithromycin dihydrate*	157.23	209.613	262.05	314.46	524.10	628.93
Pregelatinized starch**	16.20	21.60	27.00	32.40	54.00	64.80
Calcium phosphate dibasic, anhydrous	83.305	111.01	138.84	166.61	277.68	333.21
Sodium croscarmellose	5.400	7.200	9.00	10.80	18.00	21.60

TABLE VII-continued

Examples of azithromycin tablet formulations which do not exhibit a food effect.

Component	WEIGHT (MG/TABLET) 150 MG STRENGTH	200 MG STRENGTH	250 MG STRENGTH	300 MG STRENGTH	500 MG STRENGTH	600 MG STRENGTH
Magnesium stearate/ Sodium lauryl sulfate (90/10)	7.865	10.486	13.11	15.73	26.22	31.46
Opadry@	8.1	10.8	13.5	16.2	27.0	32.4
TOTAL	278.1	370.8	463.5	556.2	927.0	1,112.4

*Based on a theoretical potency of 95.4%.
**Starch 1500.
#e.g. Ac-Di-Sol.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifier, and lakes.

EXAMPLE 9

Additional tablet formulations of azithromycin (250 mg) are prepared which do not exhibit an adverse food effect and are described in Table VIII. The diluent in these formulations (calcium phosphate dibasic, anhydrous) may be substituted by calcium phosphate dibasic dihydrate, microcrystalline cellulose, lactose NF/BP/EP/JP, or other appropriate diluent. The lubricant in these tablets (magnesium stearate/sodium lauryl sulfate, 90/10) may be substituted by magnesium stearate and/or colloidal silica or sodium stearyl fumarate. Magnesium stearate and sodium stearyl fumarate are generally used in amounts constituting 0.5–7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1–1% of the total tablet weight. While considerable latitude in relative excipient ratios is possible, the calcium phosphate/pregelatinized starch ratio should be around 2:1 or greater. The Opadry film coat is not necessary to achieve food-independent drug exposure, but serves to improve ease-of-swallowing and tablet appearance and serves to differentiate strengths. The Opadry coat may comprise between 2–6% of the total tablet weight. Tablets at other potencies may be obtained by maintaining the approximate azithromycin/excipient ratios described in Table VIII, and increasing or decreasing total tablet weight.

TABLE VIII

Examples of azithromycin tablet formulations (250 mg) which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	262.05	262.05	262.05
Pregelatinized starch	50.0	13.9	50.0
Calcium phosphate dibasic, anh.	115.84	140.94	104.84
Sodium croscarmellose	9.0	20.0	20.0
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.50	13.50	13.50
TOTAL	463.5	463.5	463.5

@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.

EXAMPLE 10

Further 250 mg azithromycin tablet formulations are prepared which do not exhibit an adverse food effect and are presented in Tables IX and X. In these formulations, maize starch, sodium starch glycolate, and crosslinked polyvinylpyrrolidone serve as disintegrants. Calcium phosphate dibasic, lactose NF/BP/EP, and microcrystalline cellulose serve as diluents.

Magnesium stearate/sodium lauryl sulfate serves as a lubricant. Magnesium stearate/sodium lauryl sulfate may be substituted by magnesium stearate and/or colloidal silica or sodium stearyl fumarate. Magnesium stearate and sodium stearyl fumarate are generally used in amounts constituting 0.5–7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1–1% of the total tablet weight. While considerable latitude in relative excipient ratios is possible, the diluent/disintegrant ratio should be around 2:1 or greater. The Opadry film coat is not necessary to achieve food-independent drug exposure, but serves to improve ease-of-swallowing and tablet appearance. The Opadry coat may comprise between 2–6% of the total tablet weight. Tablets at other potencies are obtained by maintaining the approximate azithromycin/excipient ratios described in Tables IX and X, and increasing or decreasing total tablet weight. These formulas are illustrative, and substitutions of other disintegrants, diluents, and lubricants are possible, as known in the art.

TABLE IX

azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 4	FORMULATION 5	FORMULATION 6
Azithromycin dihydrate†	262.05	262.05	262.05
Maize starch*	13.9	27.0	50.0
Calcium phosphate, dibasic** OR Lactose NF/BP/EP/JP OR Microcrystalline cellulose	151.94	138.84	115.84
Sodium starch glycolate‡ OR Crosslinked polyvinylpyrrolidone@	9.0	9.0	9.0

TABLE IX-continued

azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 4	FORMULATION 5	FORMULATION 6
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.5	13.5	13.5
TOTAL	463.5	463.5	463.5

†Equivalent to 250 mg azithromycin.
*Also called starch NF or cornstarch
**Either anhydrous or dihydrate
#e.g. Explotab or Primojel
##e.g. PVP-XL from International Specialty Products Inc.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.

TABLE X

Examples of azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 7	FORMULATION 8	FORMULATION 9
Azithromycin dihydrate†	262.05	262.05	262.05
Maize starch*	13.9	27.0	27.0
Calcium phosphate, dibasic** OR Lactose NF/BP/EP/JP OR Microcrystalline cellulose	140.94	144.84	127.84
Sodium starch glycolate# OR Crosslinked polyvinylpyrrolidone##	20.0	3.0	20.0
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.5	13.5	13.5
TOTAL	463.5	463.5	463.5

*Also called starch NF or cornstarch
**Either anhydrous or dihydrate
#e.g. Explotab or Primojel
##e.g. PVP-XL from International Specialty Products Inc.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.
†Equivalent to 250 mg azithromycin.

EXAMPLE 11

The "Powder for Oral Suspension" formulation described in Table XI was prepared. This formulation does not exhibit an adverse food effect.

TABLE XI

A formulation for azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/GM)
Azithromycin dihydrate	47.97
Sucrose NF	579.71
Sorbitol, crystalline, powder, NF/FCC	289.86
Sodium carbonate, anhydrous, NF	18.84
Sodium benzoate, NF/FCC	4.35
Tragacanth gum powder, NF	14.49
Titanium dioxide USP	14.49
Colloidal silicon dioxide, NF	1.45
Aminoacetic acid (glycine) USP	5.80
Spray-dried Art. Strawberry #72653	15.26
Tropical apple punch #26908	7.63
Spray-dried peppermint stick #15634	0.15
TOTAL	1000.00

EXAMPLE 12

Azithromycin "Powder for Oral Suspension" formulations are prepared as illustrated in Tables XII and XIII. The unit potency of these formulations is 600 mg azithromycin/bottle, and the use potency after constitution with water is 40 mg/ml. To constitute, 0.52 ml water is added per gm of blend. 9 mL. water and 16.74 gm blend produce approximately 20 ml suspension. These formulations include 200 mg Azithromycin/bottle overfill. The listed "flavor system" may be freely substituted with other flavors which provide a pleasant taste and are stable at pH 10 over the shelf-life of the constituted suspension (approximately 5 days). The dye may also be freely substituted. The formulations in this Example are illustrative, and not limiting. These formulations do not exhibit an adverse food effect.

TABLE XII

Examples of formulations of Azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/BOTTLE) FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	838.57	838.57	838.57
Sucrose NF	15487.74	15370.54	15487.74
Sodium phosphate tribasic anhydrous	70.01	70.01	70.01
Hydroxypropyl-cellulose	26.62	26.62	0
Xanthan gum	26.62	26.62	0
Sodium carboxy-methylcellulose	0	0	53.24
Colloidal silicon dioxide	0	16.74	0
Glycine	0	100.46	0
Spray-dried cherry #11929	59.94	59.94	59.94
Art. Creme de Vanilla #11489	133.28	133.28	133.28
Spray-dried Art. Banana #15225	99.96	99.96	99.96
FD&C Red #40	0.67	0.67	0.67
TOTAL	16743.41	16743.41	16743.41

TABLE XIII

Examples of formulations of Azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/BOTTLE FORMULATION 4	FORMULATION 5	FORMULATION 6
Azithromycin dihydrate	838.57	838.57	838.57
Sorbitol	15138.55	7743.87	7656.37
Sucrose NF	0	7743.87	7656.37
Sodium carbonate, anhydrous, NF	302.00	0	150.00
Sodium phosphate tribasic anhydrous	0	70.01	35.00
Hydroxypropyl-cellulose	0	26.62	17.75
Xanthan gum	0	26.62	17.75
Sodium carboxy-methylcellulose	53.24	0	17.75
Colloidal silicon dioxide	16.74	0	10.00
Glycine	100.46	0	50.00
Spray-dried cherry #11929	59.94	59.94	59.94
Art. Cream de Vanilla #11489	133.28	133.28	133.28
Spray-dried Art. Banana #15223	99.96	99.96	99.96
FD&C Red #40	0.67	0.67	0.67
TOTAL	16743.41	16743.41	16743.41

EXAMPLE 14

The following formulations of unit dose packets of azithromycin are prepared as being exemplary, not limiting, of the invention (Tables XIV and XV). The flavor system for these dosage forms may be freely substituted with any flavor system which provides a pleasant taste when the contents of the packet are reconstituted in water or an aqueous beverage. When constituted in water or an aqueous beverage, these dosage forms do not exhibit an adverse food effect.

TABLE XIV

Examples of unit dose packet formulations.

COMPOSITION	FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	1.048	1.048	1.048
sucrose	9.707	9.707	5.0
sorbitol	0	0	0
sodium phosphate tribasic, anhydrous	0.04	0.2	0.088
sodium carbonate, anhydrous	0	0	0
glycine	0	0	0
colloidal silicon dioxide	0.022	0.22	0.055
Spray-dried art. cherry #11929	0.038	0.038	0.038
Spray-dried art. banana #15223	0.064	0.064	0.064

TABLE XV

Examples of unit dose packet formulations.

COMPOSITION	FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	1.048	1.048	1.048
sucrose	0	4.85	4.85
sorbitol	9.707	4.85	4.85
sodium phosphate tribasic, anhydrous	0.088	0.088	0.044
sodium carbonate, anhydrous	0	0	0.022
glycine	0	0	0.022
colloidal silicon dioxide	0.055	0.055	0.055
Spray-dried art. cherry #11929	0.038	0.038	0.038
Spray-dried art. banana #15223	0.064	0.064	0.064

What is claimed is:

1. An oral dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

2. A dosage form as defined in claim 1, wherein said mammal is a human.

3. A dosage form as defined in claim 1, further comprising a flavoring agent.

4. An oral dosage form of azithromycin which is in the form of a powder for oral suspension containing anhydrous buffer, which is administrable to a mammal that has eaten, which comprises azithromycin, one or more thickening agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

5. A dosage form as defined in claim 4, wherein said mammal is a human.

6. A dosage form as defined in claim 4, further comprising a flavoring agent.

7. A dosage form as defined in claim 6, wherein said flavoring agent is a flavor system consisting of cherry, vanilla, and banana.

8. A dosage form as defined in claim 4, in the form of a suspension made from said powder.

9. An oral dosage form of azithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has eaten, which

comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

18. A dosage form as defined in claim 9, wherein said mammal is a human.

11. A dosage form as defined in claim 9, further comprising an anhydrous buffer.

12. A dosage form as defined in claim 9, wherein said dispersing agent is colloidal silicon dioxide.

13. A dosage form as defined in claim 9, in the form of a suspension made from said unit dose packet.

14. An oral dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

15. A dosage form as defined in claim 14, wherein said mammal is a human.

16. A dosage form as defined in claim 14, further comprising a flavoring agent.

17. An oral dosage form of azithromycin which is in the form of a powder for oral suspension containing an anhydrous buffer, which is administrable to a mammal that has eaten, which comprises azithromycin, one or more thickening agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

18. A dosage form as defined in claim 17, wherein said mammal is a human.

19. A dosage form as defined in claim 17, further comprising a flavoring agent.

20. A dosage form as defined in claim 19, wherein said flavoring agent is a flavoring system consisting of cherry, vanilla, and banana.

21. A dosage form as defined in claim 17, in the form of a suspension made from said powder.

22. An oral dosage form of azithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has eaten, which comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

23. A dosage form as defined in claim 22, wherein said mammal is a human.

24. A dosage form as defined in claim 22, further comprising an anhydrous buffer.

25. A dosage form as defined in claim 22, wherein said dispersing agent is colloidal silicon dioxide.

26. A dosage form as defined in claim 22, in the form of a suspension made from said unit dose packet.

27. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
6.0% pregelatinized starch;
30.9% anhydrous dibasic calcium phosphate;
2.0% sodium croscarmellose; and
2.9% lubricant.

28. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
11.1% pregelatinized starch;
25.7% anhydrous dibasic calcium phosphate;
2.0% sodium croscarmellose; and
2.9% lubricant.

29. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
3.1% pregelatinized starch;
31.3% anhydrous dibasic calcium phosphate;
4.4% sodium croscarmellose; and
2.9% lubricant.

30. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
11.1% pregelatinized starch;
23.3% anhydrous dibasic calcium phosphate;
4.4% sodium croscarmellose; and
2.9% lubricant.

31. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
3.1% maize starch;
33.8% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

32. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
30.9% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

33. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
11.1% maize starch;
25.7% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

34. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
3.1% maize starch;
31.3% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

35. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;

32.2% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
0.7% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

36. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
28.4% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

37. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
92.5% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylcellulose;
0.2% xanthan gum;
trace coloring; and
1.8% flavoring.

38. A dosage form as defined in claim 4, comprising:
4.8% azithromycin dihydrate;
58.0% sucrose;
29.0% sorbitol;
1.9% anhydrous sodium carbonate;
0.4% sodium benzoate;
1.5% tragacanth gum powder;
1.5% titanium dioxide;
1.15% colloidal silicon dioxide;
0.6% glycine; and
2.3% flavoring.

39. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
91.8% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylcellulose;
0.2% xanthan gum;
0.1% colloidal silicon dioxide;
0.6% glycine;
trace coloring; and
1.8% flavoring.

40. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
92.5% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.3% sodium carboxymethylcellulose;
trace coloring; and
1.8% flavoring.

41. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
90.4% sorbitol;
1.8% anhydrous sodium carbonate;
0.3% sodium carboxymethylcellulose;
0.1% colloidal silicon dioxide;
0.6% glycine;
trace coloring; and
1.8% flavoring.

42. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
46.3% sorbitol;
46.3% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylmethylcellulose;
0.2% xanthan gum; and
trace coloring
1.8% flavoring.

43. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
45.7% sucrose;
45.7% sorbitol;
0.9% anhydrous sodium carbonate;
0.2% anhydrous tribasic sodium phosphate;
0.1% hydroxypropylmethylcellulose;
0.1% xanthan gum;
0.1% sodium carboxymethylcellulose;
0.1% colloidal silicon dioxide;
0.3% glycine;
trace coloring; and
1.8% flavoring.

44. A dosage form as defined in claim 9, comprising:
9.5% azithromycin dihydrate;
88.2% sucrose;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

45. A dosage form as defined in claim 9, comprising:
9.5% azithromycin dihydrate;
88.2% sorbitol;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

46. A dosage form as defined in claim 9, comprising:
9.6% azithromycin dihydrate;
88.9% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% colloidal silicon dioxide; and
0.9% flavoring.

47. A dosage form as defined in claim 9, comprising:
9.3% azithromycin dihydrate;
86.1% sucrose;
1.8% anhydrous tribasic sodium phosphate;
2.0% colloidal silicon dioxide; and
0.9% flavoring.

48. A dosage form as defined in claim 9, comprising:
16.7% azithromycin dihydrate;
79.5% sucrose;
1.4% anhydrous tribasic sodium phosphate;
0.9% colloidal silicon dioxide; and
1.6% flavoring.

49. A dosage form as defined in claim 9, comprising:
9.5% azithromycin dihydrate;
44.1% sucrose;
44.1% sorbitol;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and

0.9% flavoring.

50. A dosage form as defined in claim 9, comprising:
9.5% azithromycin dihydrate;
44.1% sucrose;
44.1% sorbitol;
0.4% anhydrous tribasic sodium phosphate;
0.2% anhydrous sodium carbonate;
0.2% glycine;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

51. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
6.0% pregelatinized starch;
30.9% anhydrous dibasic calcium phosphate;
2.0% sodium croscarmellose; and
2.9% lubricant.

52. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
11.1% pregelatinized starch;
25.7% anhydrous dibasic calcium phosphate;
2.0% sodium croscarmellose; and
2.9% lubricant.

53. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
3.1% pregelatinized starch;
31.3% anhydrous dibasic calcium phosphate;
4.4% sodium croscarmellose; and
2.9% lubricant.

54. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
11.1% pregelatinized starch;
23.3% anhydrous dibasic calcium phosphate;
4.4% sodium croscarmellose; and
2.9% lubricant.

55. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
3.1% maize starch;
33.8% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

56. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
30.9% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

57. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
11.1% maize starch;
25.7% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

58. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
3.1% maize starch;
31.3% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

59. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
32.2% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
0.7% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

60. A dosage form as defined in claim 14, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
28.4% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

61. A dosage form as defined in claim 17, comprising:
5.0% azithromycin dihydrate;
92.5% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylcellulose;
0.2% xanthan gum;
trace coloring; and
1.8% flavoring.

62. A dosage form as defined in claim 17, comprising:
4.8% azithromycin dihydrate;
58.0% sucrose;
29.0% sorbitol;
1.9% anhydrous sodium carbonate;
0.4% sodium benzoate;
1.5% tragacanth gum powder;
1.5% titanium dioxide;
1.15% colloidal silicon dioxide;
0.6% glycine; and
2.3% flavoring.

63. A dosage form as defined in claim 17, comprising:
5.0% azithromycin dihydrate;
91.8% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylcellulose;
0.2% xanthan gum;
0.1% colloidal silicon dioxide;
0.6% glycine;
trace coloring; and
1.8% flavoring.

64. A dosage form as defined in claim 17, comprising:
5.0% azithromycin dihydrate;
92.5% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.3% sodium carboxymethylcellulose;
trace coloring; and

1.8% flavoring.

65. A dosage form as defined in claim 17, comprising:

5.0% azithromycin dihydrate;

90.4% sorbitol;

1.8% anhydrous sodium carbonate;

0.3% sodium carboxymethylcellulose;

0.1% colloidal silicon dioxide;

0.6% glycine;

trace coloring; and

1.8% flavoring.

66. A dosage form as defined in claim 17, comprising:

5.0% azithromycin dihydrate;

46.3% sorbitol;

46.3% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.2% hydroxypropylmethylcellulose;

0.2% xanthan gum; and

trace coloring

1.8% flavoring.

67. A dosage form as defined in claim 17, comprising:

5.0% azithromycin dihydrate;

45.7% sucrose;

45.7% sorbitol;

0.9% anhydrous sodium carbonate;

0.2% anhydrous tribasic sodium phosphate;

0.1% hydroxypropylmethylcellulose;

0.1% xanthan gum;

0.1% sodium carboxymethylcellulose;

0.1% colloidal silicon dioxide;

0.3% glycine;

trace coloring; and

1.8% flavoring.

68. A dosage form as defined in claim 22, comprising:

9.5% azithromycin dihydrate;

88.2% sucrose;

0.8% anhydrous tribasic sodium phosphate;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

69. A dosage form as defined in claim 22, comprising:

9.5% azithromycin dihydrate;

88.2% sorbitol;

0.8% anhydrous tribasic sodium phosphate;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

70. A dosage form as defined in claim 22, comprising:

9.6% azithromycin dihydrate;

88.9% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.2% colloidal silicon dioxide; and

0.9% flavoring.

71. A dosage form as defined in claim 22, comprising:

9.3% azithromycin dihydrate;

86.1% sucrose;

1.8% anhydrous tribasic sodium phosphate;

2.0% colloidal silicon dioxide; and

0.9% flavoring.

72. A dosage form as defined in claim 22, comprising:

16.7% azithromycin dihydrate;

79.5% sucrose;

1.4% anhydrous tribasic sodium phosphate;

0.9% colloidal silicon dioxide; and

1.6% flavoring.

73. A dosage form as defined in claim 22, comprising:

9.5% azithromycin dihydrate;

44.1% sucrose;

44.1% sorbitol;

0.8% anhydrous tribasic sodium phosphate;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

74. A dosage form as defined in claim 22, comprising:

9.5% azithromycin dihydrate;

44.1% sucrose;

44.1% sorbitol;

0.4% anhydrous tribasic sodium phosphate;

0.2% anhydrous sodium carbonate;

0.2% glycine;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

75. A therapeutic package, comprising

a container,

an oral dosage form of azithromycin which exhibits either or both of:

(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm; and/or

(b) a value of $(AUC_{test})/(AUC_{std})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75,

and, associated with said package, written matter non-limited as to whether the dosage form can be taken with or without food.

76. A therapeutic package as defined in claim 75, wherein said dosage form is in the form of a tablet.

77. A therapeutic package as defined in claim 75, wherein said dosage form is in the form of a powder for oral suspension.

78. A therapeutic package as defined in claim 77, wherein said dosage form is in the form of a suspension made from said powder.

79. A therapeutic package as defined in claim 75, wherein said dosage form is in the form of a unit dose packet.

80. A therapeutic package as defined in claim 79, wherein said dosage form is in the form of a suspension made from said unit dose packet.

81. A method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an oral dosage form which exhibits either or both of:

(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm; and/or

(b) a value of $(AUC_{test})/(AUC_{std})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

82. A method as defined in claim 81, wherein said mammal is a human.

83. A method as defined in claim 82, wherein said dosage form exhibits a value of $(AUC_{fast})/(AUC_{fed})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

84. A method as defined in claim 82, wherein said dosage form is in the form of a tablet.

85. A method as defined in claim 82, wherein said dosage form is in the form of a powder for oral suspension.

86. A method as defined in claim 85, wherein said dosage form is in the form of a suspension made from said powder.

87. A method as defined in claim 82, wherein said dosage form is in the form of a unit dose packet.

88. Method as defined in claim 87, wherein said dosage form is in the form of a suspension made from said unit dose packet.

89. A method as defined in claim 83, wherein said dosage form is in the form of a tablet.

90. A method as defined in claim 89, wherein said dosage form is in the form of a powder for oral suspension.

91. A method as defined in claim 90, wherein said dosage form is in the form of a suspension made from said powder.

92. A method as defined in claim 83, wherein said dosage form is in the form of a unit dose packet.

93. A method as defined in claim 92, wherein said dosage form is in the form of a suspension made from said unit dose packet.

94. A package as defined in claim 75, wherein said dosage form exhibits a value of $(AUC_{fast})/(AUC_{fed})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

95. A package as defined in claim 94, wherein said dosage form is in the form of a tablet.

96. A package as defined in claim 94 wherein said dosage form is in the form of a powder for oral suspension.

97. A package as defined in claim 96, wherein said dosage form is in the form of a suspension made from said powder.

98. A package as defined in claim 94, wherein said dosage form is in the form of a unit dose packet.

99. A package as defined in claim 98, wherein said dosage form is in the form of a suspension made from said unit dose packet.

* * * * *

EXHIBIT B

US006268489B1

(12) **United States Patent**
Allen et al.

(10) **Patent No.: US 6,268,489 B1**
(45) **Date of Patent: Jul. 31, 2001**

(54) **AZITHROMYCIN DIHYDRATE**

(75) Inventors: **Douglas J. M. Allen**, New London; **Kevin M. Nepveux**, Old Saybrook, both of CT (US)

(73) Assignee: **Pfizer Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: 07/994,040

(22) Filed: Dec. 21, 1992

Related U.S. Application Data

(63) Continuation of application No. 07/449,961, filed on Dec. 11, 1989, now abandoned.

(30) **Foreign Application Priority Data**

Jul. 9, 1987 (WO) PCT/US87/01612

(51) **Int. Cl.**[7] **C07H 17/08**
(52) **U.S. Cl.** 536/7.4; 536/18.5
(58) **Field of Search** 536/7.4, 18.5

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,020,270		4/1977	Arcamone et al.	536/18
4,219,641	*	8/1980	Deposato et al.	536/7.2
4,474,768	*	10/1984	Bright	514/29
4,512,982	*	4/1985	Hauske et al.	536/7.2
4,517,359		5/1985	Kobrehel et al.	536/7.4
4,526,889		7/1985	Bright	514/29
4,963,531		10/1990	Remington	514/29

OTHER PUBLICATIONS

Pelizza et al., Farmaco–Ed.Sc., 31, 254–262 (1976).
Allen et al., J. Pharm. Sci., 67, 1087–1093 (1978).

* cited by examiner

Primary Examiner—Elli Peselev
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Gregg C. Benson; Mervin E. Brokke

(57) **ABSTRACT**

Non-hygroscopic, azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) dihydrate and a process therefor.

3 Claims, No Drawings

AZITHROMYCIN DIHYDRATE

This is a continuation of application Ser. No. 07/449,961, filed on Dec. 11, 1989 now abandoned as a request for U.S. examination of International Application No. PCT/US87/01612, filed Jul. 9, 1987.

BACKGROUND OF THE INVENTION

The present invention is directed to a valuable new form of azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A), viz., a non-hygroscopic dihydrate form thereof.

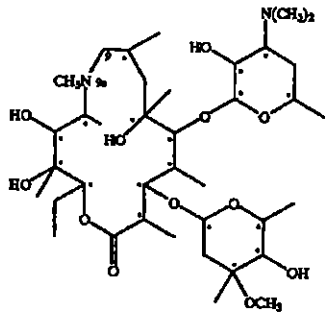
Azithromycin is the U.S.A.N. (generic name) for 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, a broad spectrum antibacterial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. The name "N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A" was employed in these patents. The present more systematic name is based upon the ring expansion and replacement nomenclature of the "IUPAC Nomenclature of Organic Chemistry, 1979 Edition," Pergamon Press, 1979, pp. 68–70, 459, 500–503.

As previously crystallized from ethanol and water (e.g., Example 3 of U.S. Pat. No. 4,474,768), azithromycin was obtained as a hygroscopic monohydrate (for details, see Preparation 1 below). Because of its hygroscopic nature, it is most difficult to prepare and maintain this prior monohydrate product in a form having a constant, reproducible water-content. It is particularly difficult to handle during formulation, since at higher relative humidity levels which are generally required to avoid electrostatic problems (e.g., flow rates, dusting with potential for explosion), the monohydrate readily picks up varying amounts of water, the amount depending upon exposure time and the precise value of the relative humidity (see Preparation 1 below). Such problems have been overcome by the present invention of a stable dihydrate which is essentially non-hygroscopic under conditions of relative humidity conducive to formulation of azithromycin.

SUMMARY OF THE INVENTION

The present invention is directed to a valuable new form of azithromycin, viz., a crystalline, non-hygroscopic dihydrate, prepared by crystallization from tetrahydrofuran and an aliphatic (C_5–C_7)hydrocarbon in the presence of at least two molar equivalents of water.

Azithromycin is of the formula



It is derived from erythromycin A without involvement of asymmetric centers, and so has stereochemistry at each of these centers (*) which is identical with that of erythromycin A. Named systematically as an erythromycin A derivative, the compound is called 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A. Azithromycin, including the present dihydrate, possess broad-spectrum antibacterial activity useful in the treatment of susceptible bacterial infections in mammals, including man.

The expression "aliphatic (C_5–C_7)hydrocarbon" refers to lower boiling hydrocarbon solvents, frequently mixtures of particular boiling point ranges such as those generally referred to as "pentane", "hexane", "hexanes", etc., but which may also be substantially pure, e.g., n-hexane, cyclohexane or methylcyclohexane. A preferred hydrocarbon solvent is so-called "hexane", having a boiling point which ranges near that of pure n-hexane.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is readily carried out. Azithromycin, prepared according to Bright or Kobrehel et al. (cited above) in amorphous form, or as the monohydrate (which may contain, because of its hygroscopicity, more than one molar equivalent of water) is dissolved in tetrahydrofuran. Since the temperatures required for the initial stages of the present process are not critical, ambient temperatures are generally employed, avoiding the cost of heating and cooling. Furthermore, to maximize yield and minimize solvent, labor and equipment costs, the volume of tetrahydrofuran is kept to a near minimum, e.g., 2 liters of solvent per kilogram of substrate. Any insoluble impurities which may be present at this stage are readily removed by conventional methods of filtration. If necessary, the mixture can be decolorized with activated carbon. If desired, the highly concentrated mixture can be diluted with a portion of (C_5–C_7)hydrocarbon prior to filtration, in order to facilitate handling. If the water content of the ingoing bulk is much greater than one molar equivalent, e.g., approaching 2-molar equivalents, it is preferable to dry the mixture for a short period of time over a drying agent such as $MgSO_4$, particularly if hydrocarbon solvent is to be added prior to filtration. To obtain the crystalline dihydrate, water is added to the resulting clear solution, in an amount sufficient to bring the total water content to a level corresponding to at least two molar equivalents, generally not exceeding a level of about 3–4 molar equivalents. The level of water present in the

system is readily monitored by standard Karl Fischer titration. The addition of water is followed by the addition of the hydrocarbon solvent (or of more hydrocarbon solvent, if the mixture was previously diluted before filtration), leading to crystallization of the desired dihydrate product. This stage of the process can be carried out at ambient temperature (e.g. 17–30° C.), but to facilitate the initial crystallization, is preferably carried at slightly elevated temperature (e.g. 30–40° C.). The total volume of hydrocarbon solvent employed is generally at least about four times in volume that of the tetrahydrofuran. Higher volumes of hydrocarbon are satisfactory, but are generally avoided in the interest of minimizing cost. Once crystallization is complete, the product is recovered by filtration, usually after a period of granulation (e.g., 3–24 hours) at ambient temperature. The product is usually vacuum dried of organic solvents (at 20–40° C., conveniently at ambient temperature). To avoid loss of water of hydration, the volatiles and water-content are generally monitored during drying, such that the level of tetrahydrofuran and hydrocarbon will generally fall below 0.25% and the water content will be within 0.3% of theory (4.6%).

Azithromycin dihydrate is formulated and administered in the treatment of susceptible bacterial infections in man according to methods and in amounts previously detailed by Bright, U.S. Pat. No. 4,474,768, cited above and hereby incorporated by reference.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

EXAMPLE 1

Non-Hygroscopic Azithromycin Dihydrate

Method A

The hygroscopic monohydrate of Preparation 1 (100 g; water-content:3.1%), tetrahydrofuran (220 ml) and diatomaceous earth (5 g) were combined in a 500 ml Erlenmyer flask, stirred for 30 minutes and filtered with 20 ml of tetrahydrofuran wash. The combined filtrate and wash was transferred to a 3 liter round bottom flask. The solution was stirred vigorously and H_2O (2.0 ml) was added. After 5 minutes, hexane (1800 ml) was added over 5 minutes, with continued vigorous stirring. Following an 18 hour granulation period, title product was recovered by filtration with 1×10 ml hexane wash, and dried in vacuo to 4.6±0.2% H_2O by Karl Fischer, 89.5 g.

Method B

The hygroscopic monohydrate of Preparation 1 (197.6 g) and tetrahydrofuran (430 ml) were charged to a reactor and the mixture stirred to achieve a milky white solution. Activated carbon (10 g) and diatomaceous earth (10 g) were added and the mixture stirred for 15 minutes, then diluted with 800 ml of hexane and filtered with suction over a pad of diatomaceous earth with 250 ml of hexane for wash. The combined filtrate and wash was diluted to 2500 ml with hexane and warmed to 34° C. With stirring, 24.7 ml of H_2O was added. The mixture was allowed to cool to room temperature, granulated for five hours and title product recovered and dried as in Method A, 177.8 g.

The dihydrate melts sharply at 126° C. (hot stage, 10°/minute); differential scanning calorimetry (heating rate, 20° C./minute) shows an endotherm at 127° C.; thermal gravimetric analysis (heating rate 30° C./minute) shows a 1.8% weight loss at 100° C. and a 4.3% weight loss at 150° C.; ir (KBr) 3953, 3553, 3488, 2968, 2930, 2888, 2872, 2827, 2780, 2089, 1722, 1664, 1468, 1426, 1380, 1359, 1344, 1326, 1318, 1282, 1270, 1252, 1187, 1167, 1157, 1123, 1107, 1082, 1050, 1004, 993, 977, 955, 930, 902, 986, 879, 864, 833, 803, 794, 775, 756, 729, 694, 671, 661, 637, 598, 571, 526, 495, 459, 399, 374, 321 and 207 cm^{-1}; [alpha]$^{26}_D$=41.4° (c=1, $CHCl_3$).

Anal. Calcd. for $C_{38}H_{72}N_2O_{12}.2H_2O$: C, 58.14; H, 9.77; N, 3.57; OCH_3, 3.95; H_2O, 4.59. Found: C, 58.62; H, 9.66; N, 3.56; OCH_3, 4.11; H_2O, 4.49. Neutralization Equivalent (0.5N HCl in 1:1 CH_3CN:H_2O): Calcd.: 374.5. Found: 393.4.

Samples of a dihydrate, slightly over dried to contain 4.1% water (less than theoretical) rapidly picked-up water at 33%, 75% or 100% relative humidities to achieve the theoretical water content (4.6%) for the dihydrate. At 33% and 75% relative humidities, water content remained essentially constant for at least 4 days. At 100% relative humidity, the water content further rose to about 5.2, where it remained essentially constant of the next three days.

A sample of the same dihyrate, maintained at 18% relative humidity gradually lost water. At four days, the water content was 2.5% and at 12 days, 1.1%.

PREPARATION 1

Hygroscopic Azithromycin Monohydrate

Substantially following the methylation procedure of Kobrehel et al., U.S. Pat. No. 4,517,359; and the crystallization procedure of Bright, U.S. Pat. No. 4,474,768; 9-deoxo-9a-aza-9a-homoerythromycin A (previously called 11-aza-10-deoxo-10-dihydroerythromycin A; 100 g, 0.218 mol) was dissolved with stirring in 400 ml $CHCl_3$. Formic acid (98%; 10.4 ml, 0.436 mol) and formaldehyde (37%; 16.4 ml, 0.349 mol) were added over 4–5 minutes, and the mixture heated at reflux for 20 hours. The mixture was cooled to ambient temperature, diluted with 400 ml H_2O and adjusted to pH 10.5 with 50% NaOH. The aqueous layer was separated and extracted 2×100 ml with fresh $CHCl_3$. The organic layers were combined, stripped in vacuo to 350 ml, twice diluted with 450 ml of ethanol and restripped to 350 ml, and finally diluted with 1000 ml H_2O over a 1 hour period, pausing for 15 minutes as a slurry began to develop after the addition of about 250 ml of H_2O. Title product was recovered by filtration and dried in air at 50° C. for 24 hours, 85 g; mp 136° C.; differential thermal analysis (heating rate 20° C./minute) shows an endotherm at 142° C.; thermal gravimetric analysis (heating rate 30° C./minute) shows a 2.6% weight loss at 100° C. and a 4.5% weight loss at 150° C.; water content 3.92%; ethanol content 1.09%.

Anal. Calcd. for $C_{38}H_{72}N_2O_{12}$ (corrected for ethanol and water content): C, 58.46; H, 9.78; N, 3.74; Alkoxy, 4.67. Found: C, 58.40; H, 9.29; N, 3.50; Alkoxy, 4.52.

A sample of the monohydrate (having a water content of 3.2%) was maintained at 18% relative humidity for 14 days. The sample lost water over the first 24 hours to yield monohydrate having the theoretical water content (2.35%). The water content then remained substantially constant over 14 days, a value of 2.26% being recorded at 14 days.

At 33% relative humidity the water content of a sample of the same monohydrate rapidly rose to 5.6% where it remained substantially steady for at least three days. Similarly at 75% and 100% relative humidity, the water content rose rapidly, but was now maintained at even higher levels, 6.6% and 7.2%, respectively, for at least 3 days.

What is claimed is:

1. Crystalline azithromycin dihydrate.

2. A method of preparing crystalline azithromycin dihydrate which comprises crystallization of amorphous azithromycin or azithromycin monohydrate from a mixture of tetrahydrofuran and a (C_5–C_7) aliphatic hydrocarbon in the presence of at least 2 molar equivalents of water.

3. A method of claim 2 wherein the hydrocarbon is hexane.

* * * * *

EXHIBIT C

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August 5, 2003

By Hand

Jeffrey B. Kindler, Esq.
Senior Vice President and General Counsel
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5575

Re: Azithromycin - U.S. Patent Nos. 5,605,889 and 6,268,489

Dear Mr. Kindler:

We represent Teva Pharmaceuticals USA, Inc ("Teva"). We write concerning U.S. Patent Nos. 5,605,889 ("the '889 patent"), entitled "Method of Administering Azithromycin," and 6,268,489 ("the '489 patent"), entitled "Azithromycin Dihydrate," both of which are assigned on their face to Pfizer, Inc.

On December 12, 2002, Teva filed with the FDA Abbreviated New Drug Application ("ANDA") No. 65-153 for 250 mg azithromycin tablets. On November 27, 2002, Teva filed ANDA No. 65-150 for 600 mg azithromycin tablets. Teva expects the FDA to approve these ANDAs in due course.

By filing these ANDAs, Teva has made substantial preparations to make, use, offer to sell, sell, and/or import a generic version of ZITHROMAX®. By filing these ANDAs with the intent to obtain approval to market prior to the expiration of the '489 and '889 patents, Teva has committed a technical act of infringement of these patents. In light of these activities, Teva requests that Pfizer grant a covenant to Teva that Pfizer will not enforce the '889 and '489 patents against Teva for having made, making, using, offering for sale, selling, or importing the azithromycin tablets described in Teva's ANDA Nos. 65-153 and 65-150.

Pfizer has sued Novopharm, Teva's Canadian affiliate on the Canadian equivalent of the '489 patent. Based on the information available to Pfizer as a result of that suit, Teva believes that Pfizer has sufficient information to determine whether it believes Teva's manufacture, use, importation, or sale of the azithromycin products covered by the ANDAs infringe the '889 and/or '489 patents. However, should you require further information, Teva will provide to Pfizer, upon execution of an appropriate confidentiality agreement, information regarding the formulation of the products described in Teva's ANDAs, the bioequivalency data included in the ANDAs, and samples of (i) the products described in the ANDAs, (ii) the raw materials used to make those products, and (iii) azithromycin ethanolate monohydrate, the active ingredient in the products described in the ANDAs.

We are prepared to send Pfizer these materials immediately upon execution of an appropriate confidentiality agreement. For your convenience, we attach a form confidentiality agreement. However, we will disclose these materials under any reasonable terms. If our letter is unsatisfactory, please propose an acceptable alternative.

In view of the urgent need to resolve issues of potential patent infringement prior to Teva's marketing of its azithromycin products, we ask that you respond to this letter **within forty five (45) days** of receipt. If we do not receive a reply within this time frame, we will take appropriate legal action.

Very truly yours,

Steven J. Lee

cc: Richard Egosi, Esq.

Enclosure

CONFIDENTIALITY AGREEMENT

This Confidentiality Agreement is executed by and between TEVA Pharmaceuticals USA ("Teva"), PFIZER, INC. ("Pfizer"), and Counsel therefore.

RECITALS

WHEREAS, pursuant to § 505(j), Title 21 of the Federal Food, Drug and Cosmetic Act ("the Act"), Teva has filed abbreviated new drug applications, ANDA Nos. 65-153 and 65-150, to obtain approval to engage in the commercial manufacture, use, sale, and importation of azithromycin before the expiration of U.S. Patent Nos. 5,605,889 ("the '889 patent") and 6,268,489 ("the '489 patent").

WHEREAS, Pfizer owns the '889 and '489 patents.

WHEREAS, Pfizer manufactures and markets a pharmaceutical product called Zithromax® (azithromycin) and owns and/or controls certain patent rights, trademarks and know-how relating thereto, including the '889 and '489 patents.

WHEREAS, by letter dated August 5, 2003, Teva offered Pfizer certain confidential information of Teva with respect to ANDA Nos. 65-153 and 65-150 and the product Teva proposes to sell thereunder ("Teva Confidential Information") to allow Pfizer to evaluate whether it believes the commercial manufacture, use, sale, or offer for sale in the United States, or the importation into the United States of the azithromycin products described in its ANDAs will infringe, contribute to or induce the infringement of the '889 and '489 patents.

WHEREAS, Teva will provide Counsel for Pfizer with sufficient of Teva's Confidential Information to permit them to conduct an evaluation under appropriate confidentiality provisions as set forth herein.

NOW THEREFORE, in consideration of the mutual covenants herein contained, the parties mutually agree as follows:

1. Teva shall promptly provide to Counsel for Pfizer a copy of documents sufficient to describe in detail formulation of Teva's proposed azithromycin product, including but not limited to the components of the formulation, the percentage of each component used in the formulation and the process by which Teva prepares the proposed azithromycin product; one (1) 50 tablet sample from each lot of Teva's azithromycin tablets, including 250 mg and 600 mg, including one (1) 50 tablet sample from each lot which was submitted to the FDA, or as to which information was submitted to the FDA in connection with ANDAs 65-153 and 65-150, as well as samples of the raw materials used to make those tablets; and the bioequivalency data included in ANDA Nos. 65-153 and 65-150.

2. Counsel for Pfizer shall use the Teva Confidential Information referenced in Paragraph 1 herein for the sole purpose of evaluating whether it believes the commercial

manufacture, sale, or offer for sale within the United States, or the importation into the United States, of the azithromycin products described in ANDA Nos. 65-153 and 65-150 will infringe, contribute to, or induce the infringement of the '889 and '489 patents. At the conclusion of such evaluation, but in no event later than September 19, 2003, Counsel for Pfizer shall destroy or return all Teva Confidential Information.

3. Counsel for Pfizer may not disclose Teva's confidential information to Pfizer or any other party, except that Counsel for Pfizer may disclose the physical samples to Pfizer employees for the purpose of conducting in vitro tests, and may disclose any of the confidential information, including the physical samples, to independent experts not associated with Pfizer. Such experts must first be identified to Teva, and Teva must have 5 business days within which to object to such experts. Such experts must be made aware of this agreement and must agree to abide by its terms. Counsel for Pfizer agrees to not disclose, communicate or cause to be communicated to any third party, in any manner whatsoever, any and all of the Teva Confidential Information without receiving the prior written consent of Teva to use such Confidential Information. Counsel for Pfizer will not disclose any of Teva's Confidential Information for any reason whatsoever except as set forth above. Samples of Teva's azithromycin and azithromycin products are not yet approved for marketing in the United States, and may not be administered to human patients or subjects.

4. Counsel for Pfizer shall have no obligation to Teva under this Agreement to maintain the confidentiality of information that:

a. can be demonstrated to have been in the public domain prior to execution of this Agreement;

b. can be demonstrated to have been in possession, either through independent development or from another source not under obligation of secrecy to Teva prior to disclosure of Teva's Confidential information under this Agreement; or

c. becomes part of the public domain by publication or otherwise, not due to any unauthorized acts by Counsel for Pfizer.

5. Counsel for Pfizer, and any independent experts retained by them, agree to maintain the confidentiality of all of Teva's Confidential Information received under the terms of this Agreement unless instructed otherwise by Teva in writing.

6. This Agreement constitutes the entire agreement between the parties and supersedes all previous agreements and understandings relating to the subject matter hereof. This Agreement can only be modified by a writing signed by both parties hereto.

7. This Agreement may be executed by facsimile signatures and/or in counterparts and will become effective upon the date execution has been made by the last party whose execution is required, each such counterpart of which shall be an original, but all of which constitute one agreement.

ACCEPTED AND AGREED TO:

PFIZER, INC.
By:
Title: _____
Date: _____

TEVA PHARMACEUTICALS USA, INC.

By: _____
Title: _____
Date: _____

EXHIBIT B

ORIGINAL

IN THE UNITED STATES DISTRICT COURT FOR THE
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC.,

Plaintiff,

v.

PFIZER INC.,

Defendant.

Civil Action No. 09 cv 4979

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), for its Complaint against Pfizer Inc. ("Pfizer"), alleges as follows:

THE PARTIES

1. Teva is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090. Teva is a developer, manufacturer, and marketer of generic and other pharmaceutical products in the United States.

2. On information and belief, Pfizer is a Delaware corporation with its principal place of business at 235 East 42nd Street, New York, New York, 10017-5575.

3. On information and belief, Pfizer owns U.S. Patent No. 5,605,889 ("the '889 patent"), entitled "Method of Administering Azithromycin," a copy of which is attached hereto as Exhibit A.

4. On information and belief, Pfizer owns U.S. Patent No. 6,268,489 ("the '489 patent"), entitled "Azithromycin Dihydrate," a copy of which is attached hereto as Exhibit B.

5. On information and belief, Pfizer holds New Drug Application ("NDA") No. 50-784 for ZITHROMAX® 500 mg azithromycin dihydrate ("azithromycin") tablets.

JURISDICTION AND VENUE

6. This Court has original jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), in that it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 *et seq.*

7. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction seeking a declaratory judgment that the '889 and '489 patents are invalid and not infringed.

8. Personal jurisdiction exists over the defendant because defendant has its principal place of business within this district, and because defendant does business within this district.

9. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and 1400(b).

THE PRESENCE OF AN ACTUAL CONTROVERSY

10. Pfizer markets in the U.S. an oral antibiotic under the trade name ZITHROMAX®. The active ingredient in ZITHROMAX® is azithromycin. In its 2002 Annual Report, Pfizer reported sales of ZITHROMAX® of over $1.5 billion. In its 2003 Annual Report, Pfizer reported sales of ZITHROMAX® of over $2 billion.

11. On October 9, 2003, Teva filed Abbreviated New Drug Application ("ANDA") Number 65-193 ("ANDA No. 65-193"). ANDA No. 65-193 is directed to a generic version of ZITHROMAX® 500 mg tablets. By preparing and filing this ANDA, Teva has made substantial preparation to make, use, import, offer to sell, and sell a generic version of 500 mg ZITHROMAX® tablets in the U.S.

12. Pfizer's '889 and '489 patents contain claims directed to azithromycin. On information and belief, Pfizer will bring suit against Teva, alleging infringement of the '889 and '489 patents, if Teva commercially markets generic versions of 500 mg ZITHROMAX® tablets.

13. Pfizer has demonstrated a willingness and intention to enforce foreign patents that are related to ZITHROMAX®. Pfizer initiated proceedings in Canada against Novopharm, an affiliate of Teva, asserting the Canadian equivalents to the '489 and '889 patents. *Pfizer Canada and Pfizer Inc. v. Novopharm*, Federal Court – Trial Division, Ontario, Court File No. T-74-03; *Pfizer Canada and Pfizer Inc. v. Novopharm*, Federal Court – Trial Division, Ontario, Court File No. T-2448-03. In addition, Pfizer has initiated proceedings against other entities that have indicated an intention to market generic equivalents of ZITHROMAX® in Canada.

14. Moreover, Pfizer previously refused to grant Teva a covenant that it will not enforce the '889 and '489 patents against Teva. On November 27, 2002 and December 12, 2002, Teva filed ANDA Nos. 65-150 and 65-153, respectively, seeking approval to market generic versions of 250 mg and 600 mg ZITHROMAX®. On August 5, 2003, Teva hand delivered to Pfizer a letter ("the August 5, 2003 letter") requesting a covenant that Pfizer will not enforce the '889 and '489 patents against Teva. (A copy of the August 5, 2003 letter is attached as Exhibit C.) Teva requested that Pfizer respond to the August 5, 2003 letter within forty-five days of receipt. Pfizer did not respond within the forty-five days, and indeed Teva has received no response from Pfizer to date.

15. On September 22, 2003, Teva filed suit against Pfizer in this Court, seeking a declaratory judgment of invalidity of the '889 and '489 patents, and/or a declaratory judgment of noninfringement with regard to Teva's generic version of ZITHROMAX® 250 and 600 mg tablets. This suit is currently pending under Civil Action No. 03CV7423 (LAP)(AJP).

16. Furthermore, Pfizer (or its predecessor) has demonstrated its intention to prevent generic competition from Teva by attempting to enforce its patents against other products of Teva. On at least five occasions, Pfizer (or its predecessor) sued or maintained suit against Teva (or its related entities) for patent infringement relating to other drugs for which Teva has filed an ANDA: (i) *Pfizer Inc. and Pfizer Technologies Ltd. v. Novopharm Ltd.*, 00-cv-01475 (N.D. Ill.), concerning fluconazole; (ii) *Pfizer Inc./Warner-Lambert v. Teva*, 00-cv-4589 and 00-cv-4168 (D.N.J.), concerning gabapentin; (iii) *Schwarz Pharma, Inc., Schwarz Pharma AG and Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.*, 01-cv-4995 (D.N.J.), concerning moexipril; (iv) *Bayer and Pfizer v. Biovail & Teva*, 01-cv-1205 and 01-cv-1206 (D.P.R.), concerning nifedipine; and (v) *Warner-Lambert v. Teva USA*, 99-cv-0922 (D.N.J.), concerning quinipril.

17. In view of Pfizer's previous refusal to grant Teva a covenant that it will not enforce the '889 and '489 patents against Teva, Pfizer's proceedings against Teva's affiliate and others to enforce the Canadian equivalent of the '489 and '889 patents, and Pfizer's pattern of aggressively enforcing its patents in an attempt to prevent generic competition by Teva, Teva is under a reasonable apprehension that Pfizer will sue Teva, alleging infringement of the '889 and '489 patents.

18. To avoid legal uncertainty and to protect its substantial investment (and anticipated future investments) in its manufacturing process for its generic 500 mg ZITHROMAX® product, Teva has instituted this declaratory judgment action.

COUNT I
DECLARATORY JUDGMENT OF NONINFRINGEMENT

19. Teva's commercial manufacture, use, offer for sale, sale, or importation of its 500 mg azithromycin tablets pursuant to ANDA No. 65-193, or the active ingredient thereof, would not infringe any properly construed claim of the '889 patent.

COUNT II
DECLARATORY JUDGMENT OF NONINFRINGEMENT

20. Teva's commercial manufacture, use, offer for sale, sale, or importation of its 500 mg azithromycin tablets pursuant to ANDA No. 65-193, or the active ingredient thereof, would not infringe any properly construed claim of the '489 patent.

COUNT III
DECLARATORY JUDGMENT OF PATENT INVALIDITY

21. The claims of the '889 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

COUNT IV
DECLARATORY JUDGMENT OF PATENT INVALIDITY

22. The claims of the '489 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

PRAYER FOR RELIEF

WHEREFORE, Teva respectfully requests the Court enter judgment against Pfizer to include:

A. A declaration that Teva's manufacture, use or sale of its 500 mg azithromycin tablets pursuant to ANDA No. 65-193, or the active ingredient thereof, will not infringe United States Patent No. 5,605,889;

B. A declaration that Teva's manufacture, use or sale of its 500 mg azithromycin tablets pursuant to ANDA No. 65-193, or the active ingredient thereof, will not infringe United States Patent No. 6,268,489;

C. A declaration that United States Patent No. 5,605,889 is invalid;

D. A declaration that United States Patent No. 6,268,489 is invalid;

E. An award of Teva's reasonable costs and attorneys' fees in connection with this action; and

F. All such other and further relief as the Court may deem just and proper.

Respectfully submitted,

KENYON & KENYON

Dated June 23, 2004 By: _____

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Counsel for Plaintiff,
TEVA PHARMACEUTICALS USA, INC.

US005605889A

United States Patent [19]

Curatolo et al.

[11] Patent Number: 5,605,889

[45] Date of Patent: Feb. 25, 1997

[54] METHOD OF ADMINISTERING AZITHROMYCIN

[75] Inventors: William J. Curatolo, Niantic; George H. Fouldi, Waterford, both of Conn.; Hylar L. Friedman, Brattleboro, Vt.

[73] Assignee: Pfizer Inc., New York, N.Y.

[21] Appl. No.: 235,069

[22] Filed: Apr. 29, 1994

[51] Int. Cl.[6] A61K 31/70; A61K 9/14; A61K 9/20

[52] U.S. Cl. 514/29; 514/960; 424/464; 424/465; 424/474; 424/480; 424/481; 536/7.2

[58] Field of Search 514/29, 960; 536/7.2; 424/464, 465, 474, 480, 481

[56] References Cited

U.S. PATENT DOCUMENTS

4,382,085	5/1983	Sciavolino et al.	514/29
4,474,768	10/1984	Bright	514/29
4,517,359	5/1985	Kobrehel et al.	536/7.4
4,963,531	10/1990	Remington	514/29
5,250,518	10/1993	Kobrehel et al.	514/29
5,350,839	9/1994	Asaka et al.	536/7.4

FOREIGN PATENT DOCUMENTS

0307128	3/1989	European Pat. Off. .
0582396	2/1994	European Pat. Off. .

OTHER PUBLICATIONS

Curatolo et al. *J. Pharm. Sci.*, vol. 77 (4), pp. 322–324, (1988).

Welling et al. *J. Pharm. Sci.*, vol. 67 (6), pp. 764–766, (1978).

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Malmborg, A. *Curr. Med. Res. Opin.* vol. 5 (Suppl. 2), pp. 15–18, (1978).

Drew et al., Pharmacotherapy, 12, 3, 161–173 (1992).

Chu et al., J. Clin. Pharmacol., 32, 32–36 (1992).

Hopkins, S., Am. J. Med., 91 (Suppl 3A), 40S–45S (1991).

Toothaker et al., Ann. Rev. Pharmacol. Toxicol. vol. 20, 173–199, 1980.

Russell et al., Pharmaceutical Research, vol. 10, No. 2, 187–196, 1993.

CA Abstracts: vol. 120:38194s; 1994.

Zithromax (Trademark of Pfizer, Inc.) Capsules Package Insert for azithromycin capsule dosage form sold commercially in U.S.

Primary Examiner—John Kight
Assistant Examiner—Howard C. Lee
Attorney, Agent, or Firm—Peter C. Richardson; Gregg C. Benson; James T. Jones

[57] ABSTRACT

An oral dosage form of azithromycin which does not exhibit an adverse food effect; Specific azithromycin oral dosage forms including tablets, powders for oral suspensions and unit dose packets; Methods of treating microbial infections with the dosage forms; And therapeutic packages containing the dosage forms.

99 Claims, No Drawings

METHOD OF ADMINISTERING AZITHROMYCIN

This invention relates to a dosage form of azithromycin, and also to a method of treating a microbial infection which involves administering azithromycin in the fed state to a mammal, including a human patient, in need of such treatment.

BACKGROUND OF THE INVENTION

Azithromycin is the U.S.A.N. (generic name) for 9a-aza-9a-methyl-9-deoxo-9a-homoerythromycin A, a broad spectrum antimicrobial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. These patents disclose that azithromycin and certain derivatives thereof possess antibacterial properties and are accordingly useful as antibiotics.

In general, it is known that the absorption and bioavailability of any particular therapeutic agent can be affected by numerous factors when dosed orally. Such factors include the presence of food in the gastrointestinal (GI) tract because, in general, the gastric residence time of a drug is usually significantly longer in the presence of food than in the fasted state. If the bioavailability of a drug is affected beyond a certain point due to the presence of food in the GI tract, the drug is said to exhibit a "food effect". Food effects are important inasmuch as, when a drug exhibits an adverse food effect, there is risk associated with administering it to a patient who has eaten recently. The risk derives from the potential that absorption into the bloodstream may be adversely affected to the point that the patient risks insufficient absorption to remediate the condition for which the drug was administered.

Other factors can also be involved in drug bioavailability, the following being a non-comprehensive listing:

(1) The particular dosage form can affect bioavailability. For example, the gastric residence time of a tablet or capsule can be significantly longer than that of a suspension, and the difference may vary depending on whether the subject has eaten or is fasted.

(2) The pH of the stomach varies, between the fed and fasted state, with the amount of food therein, and drugs which are decomposition-sensitive to pH can be affected accordingly.

(3) The capacity of the liver to metabolize an absorbed drug (so-called "first pass" metabolism) may vary with the type of meal eaten. For example some vegetables (such as brussels sprouts) can stimulate first pass metabolism of some drugs, but not others. Grapefruit juice, on the other hand, may inhibit first pass metabolism of some drugs.

(4) Bile, which is released from the gallbladder into the small intestine when a meal is ingested, has the ability to solubilize poorly soluble drugs and thus increase bioavailability.

Additional factors can also be involved in the absorption and bioavailability of a particular drug, and absorption can actually be increased as well as decreased. These additional factors include, for example, pH-dependent solubility, site-specific intestinal permeation rate, instability to intestinal enzymes, susceptibility to first pass metabolism, and instability to colonic bacteria. Given the plethora of factors which can influence bioavailability, there usually is no way to predict, in the absence of actual testing, whether a particular drug will exhibit a food effect. For example, Toothaker and Welling, *Ann. Rev. Pharmacol. Toxicol.*, 1980, 173–99, discuss various drugs whose absorption is delayed in the presence of food (cephalexin, cefuclor, metronidazole, aspirin, diclofenac, indoprofen, digoxin, cimetidine), whose absorption may be unaffected by food (ampicillin, erythromycin estolate, spiramycin, propylthiouracil, oxazepam, hendroflumethiazide), and whose absorption is increased in the presence of food (erythromycin ethylsuccinate, nitrofurantoin, 8-methoxsalen, propranolol, metoprolol, dicoumarol, diazepam, hydrochlorothiazide).

As a further example, there appears to be no clear or definitive support for the proposition that tablets might exhibit fewer food effects than capsules, or vice-versa. Toothaker and Welling review studies which demonstrate food related reduced absorption for tablet dosage forms of erythromycin stearate, aspirin, nafcillin, and sotalol.

In the case of azithromycin, at least one (unpublished) study has shown that the absorption of azithromycin can be adversely affected if the patient is in a fed state, and it has heretofore been conventional wisdom that azithromycin capsule dosage forms exhibit a so-called adverse "food effect". Accordingly, in countries where azithromycin is currently available for use in the treatment of human patients, the product is sold with the specific direction that it be administered only in the fasted state, i.e. at least one hour before or two hours following a meal.

It would accordingly be useful if azithromycin could be administered to patients that have eaten recently and also if a dosage form for azithromycin were available which could be administered to patients that have eaten, as well as patients in a fasted state.

SUMMARY OF THE INVENTION

This invention provides an oral dosage form of azithromycin which can be administered to a mammal (including humans) that has eaten and which exhibits substantially no adverse food effect, excluding any dosage form which contains a significant amount of an alkaline earth oxide or hydroxide. The dosage form exhibits a mean $(AUC_{fed})/(AUC_{fa})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, the terms "$(AUC_{fed})/(AUC_{fa})$" and "90% confidence limit" being fully defined below.

In a further aspect, this invention provides a specific oral azithromycin dosage form which does not exhibit an adverse food effect. The dosage form comprises azithromycin and a pharmaceutically acceptable carrier, as hereinafter further detailed and described. The dosage form is in the form of a tablet (including both swallowable-only and chewable forms), in the form of a unit dose packet (sometimes referred to in the art as a "sachet"), in the form of a suspension made from a unit dose packet, in the form of a powder for oral suspension, and in the form of an oral suspension per se. It is noted that when a unit dose packet is constituted, it is probably mainly in the form of a suspension if reconstituted according to directions, although the extent of suspension versus solution depends on a number of factors such as pH. The use of the term "suspension" herein is intended to embrace liquids containing azithromycin partially in suspension and partially in solution, and also totally in solution.

In a further aspect, this invention provides a method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an oral dosage form which exhibits substantially no adverse food effect. The dosage form employed exhibits a

mean ($AUC_{f,ss}$)/($AUC_{f,ss}$) of at least 0.80 with a lower 90% confidence limit of at least 0.75.

Reference herein and in the claims to a mammal (including humans) that has "eaten" means that the mammal has eaten food of any sort within one hour prior to dosing up to two hours after dosing.

In a further aspect, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithromycin which does not exhibit an adverse food effect contained therein, and, associated with said container, written matter non-limited as to whether the dosage form can be taken with or without food.

It is noted that powders for oral suspension and unit dose packets, of course, are not ingested directly by patients; rather, they are reconstituted in a suitable vehicle. These terms are nonetheless considered to be within the penumbra of the term "dosage form" for purposes of this invention.

Capsules as a dosage form do not form a part of the invention.

For purposes of this invention azithromycin may be administered alone or in combination with other therapeutic agents.

A food effect can be detected and quantified as described, for example in Toothaker and Welling, supra, by determining the area under a curve (AUC) which plots the serum concentration (e.g., in μg/mL) of azithromycin along the ordinate (Y-axis) against time along the abscissa (X-axis). Generally, the values for AUC represent a number of values taken from all the subjects in a patient test population and are, therefore, mean values averaged over the entire test population. By measuring the area under the curve for a fed population of subjects ($AUC_{f,ss}$) and comparing it with the area for the same population of fasted subjects ($AUC_{f,ss}$), it can be determined whether a given drug exhibits an adverse food effect or not.

For definitional purposes of this invention, and specifically with respect to azithromycin dosage forms only, a dosage form of azithromycin exhibits an adverse food effect if, after dosing a population, once fasted and once fed, the mean ($AUC_{f,ss}$)/($AUC_{f,ss}$) is below the value 0.80 and/or the lower 90% confidence limit for this ratio is below 0.75.

Conversely, a dosage form of azithromycin which does not exhibit an adverse food effect is one which, when tested on a test population, exhibits a value for ($AUC_{f,ss}$)/($AUC_{f,ss}$) of at least 0.80 and a lower 90% confidence limit for this value of at least 0.75. The value for mean ($AUC_{f,ss}$)/($AUC_{f,ss}$) can have any value above 0.80 and still be within the scope of this invention, though it is preferred that it have an upper (mean) limit of 1.25, with an upper 90% confidence limit of 1.40 or below.

A population of "fed" subjects, for purposes of definition and for measuring $AUC_{f,ss}$, is one made up of subjects each of whom has eaten a Food and Drug Administration (FDA)-recommended standard high fat breakfast within a period of twenty minutes, and then ingested (i.e., swallowed) the test dosage form essentially immediately thereafter. A standard high-fat breakfast consists of, for example, two eggs fried in one tablespoon of butter, two strips of bacon, six ounces of hash brown potatoes, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces of whole milk. This standard high-fat breakfast contains approximately 964 calories, 54% supplied as fat (58 gm) and 12% supplied as protein, calculated using the monograph "Nutritive Value of Foods", U.S. Department of Agriculture Home and Garden Bulletin Number 72. Additional food can also be consumed within the twenty minute period and the subject still qualifies as "fed". A "fasted subject" for purposes of definition and for measuring $AUC_{f,ss}$ is one who has not eaten for at least eight hours, typically overnight, prior to ingestion of the dosage form.

The 90% confidence limits on $AUC_{f,ss}$/$AUC_{f,ss}$ for a particular population, in this case either a fed or a fasted population, can be (and were) calculated as described following using Schuirman's two one-sided test procedure.

The log-transformed AUCs were analyzed by means of an analysis of variance appropriate for a two-period, two-treatment crossover design. Analysis was carried out using Statistical Analysis System (SAS) software from SAS Institute, Cary, N.C. SAS procedure referred to in the SAS software as PROC GLM was used to determine sequence, subject within sequence, period and treatment (Fed/Fasted) effects. The sequence effect was tested using the [subject within sequence] mean square from the analysis of variance (ANOVA) as an error term. All other effects were tested against residual error (error mean square) from the ANOVA. The LSMEANS statement of SAS was used to calculate the least square means and their standard errors and covariances. These were used to obtain estimates for adjusted differences between treatment means and standard errors associated with these differences (log transformed).

The 90% confidence interval for two-way crossover design was constructed, based on these estimates, as the difference plus (or minus) the standard error of the difference times the 95th percentile of the t-distribution with (twice the sample size-2) degrees of freedom. The anti-log was taken on the limits to obtain the corresponding confidence for the ratio.

That a dosage form according to the invention does not exhibit an adverse food effect is surprising in view of the fact that azithromycin is unstable at low (acid) pH, on the order of the acidity encountered at the pH of stomach acid. The inventors have demonstrated that azithromycin breaks down if exposed to stomach juices which inherently exhibit acid pH. Thus, without being bound to any mechanism of action, it is surprising that rapid disintegration in the GI tract appears to be of importance to the invention.

Commonly assigned co-pending application Ser. No. 07/922,262 filed Jul. 30, 1992 discloses taste masking compositions of bitter pharmaceutical agents, such as azalide antibiotics, containing, as a taste-masking component, a basic compound selected from the group consisting of alkaline earth oxides and alkaline earth hydroxides. A composition of this invention, if it contains an alkaline earth oxide or hydroxide at all, contains less than a taste-masking amount of the taste-masking component. A composition of this invention therefore preferably contains less than about 1% of an alkaline earth oxide or hydroxide, and may be free of such taste-masking component entirely.

DETAILED DESCRIPTION

Azithromycin is typically present in formulations according to the invention in an amount of from about 25 mg to about three grams, preferably 250 mg to two grams, for treatment of a human. If dosage forms are to be used for animal/veterinary applications, the amount can, of course, be adjusted to be outside these limits depending, for example, on the size of the animal subject being treated (e.g., a horse). The term "azithromycin" includes the pharmaceutically acceptable salts thereof, and also anhydrous as well as hydrated forms. The azithromycin is preferably present as the dihydrate, disclosed, for example, in published European Patent Application 0 298 650 A2.

In order to test whether a particular azithromycin dosage form exhibits an adverse food effect, the most reliable method is actually to test the dosage form in vivo on a subject population, once fed and once fasted, determine the level of serum (or plasma) azithromycin with time, plot curves for the concentration of serum (or plasma) azithro-

mycin with time in each subject (fed and fasted) as described above, determine the area under each curve (conventionally, for example by simple integration) and finally determine whether the mean ratio (AUC_{fed})/(AUC_{fast}) exceeds 0.80, and whether the lower 90% confidence limit equals or exceeds 0.75.

It is believed that the azithromycin dosage forms of the invention do not exhibit a food effect in large part because they either provide azithromycin ready for dissolution in the GI tract essentially immediately following ingestion (suspensions), or they disintegrate rapidly following ingestion (tablets) and thereby provide azithromycin rapidly for dissolution. While not wishing to be bound by theory, it is believed that if an azithromycin dosage form provides azithromycin immediately following ingestion for dissolution in the GI tract, or at least provides azithromycin for dissolution within a certain time period following ingestion, the azithromycin will be absorbed into the bloodstream at a rate which results in substantially no adverse food effect. In order for an adequate rate of absorption to occur, it is believed that the dosage form should provide azithromycin at a rate such that at least about 90% of the azithromycin dissolves within about 30 minutes following ingestion, preferably within about 15 minutes following ingestion. A non-capsule dosage form comprising azithromycin is also considered to fall within the scope of the appended claims if it satisfies the in vitro dissolution testing requirements enumerated herein. An azithromycin dosage form according to the invention exhibits at least about 90% dissolution of azithromycin within about 30 minutes, preferably within 15 minutes, when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml approx. 0.1M dibasic sodium phosphate buffer, pH 6.0, 37° C. with paddles turning at 100 rpm. This test is described in US Pharmacopeia XXII, pp. 1578–1579. Dosage forms which pass this test under more stringent conditions (lower volume of buffer, greater amount of dosage form, lower temperature, higher pH, lower paddle speed) are also included under the above definition. Any modifications to this test are also described herein. The time required for dissolution of a particular azithromycin dosage form in this in vitro test is believed to be an indicator of the time required for dissolution of the dosage form in the GI environment. The following discussion is believed pertinent in this regard.

It is generally assumed and observed that the in vitro dissolution rate of dosage forms exhibits a rank order correlation with in vivo dissolution, particularly for a single dosage form type, e.g. tablets, which vary systematically in composition. Thus in vitro dissolution evaluation serves an important role in control of the quality of manufactured dosage forms. It is not necessarily true that the in vitro dissolution rate is exactly the same as the in vivo dissolution rate. This is not surprising, since the artificial conditions of an in vitro dissolution test (e.g. vessel geometry, stirring rate, stirring method, and so forth) are not identical to the conditions under which a dosage form disintegrates and dissolves in the GI tract.

When comparing dosage forms of different type, e.g. capsules and tablets, in vitro dissolution rate should correlate roughly with in vivo dissolution rate. However, subtle differences exist between the disintegration mechanisms of capsules and tablets. For capsules, at least partial dissolution of the gelatin shell must precede complete dissolution of the enclosed drug. Furthermore, capsule shells generally dissolve first at the capsule ends, and later at the capsule center. Tablets, on the other hand, disintegrate homogeneously. Thus subtle differences may exist in the in vitro/in vivo dissolution correlation when comparing capsules and tablets. For example, capsules and tablets which exhibit similar in vitro dissolution rates may exhibit subtle differences in in vivo dissolution rate. While such subtle differences may have no therapeutically significant effect on systemic bioavailability of an orally dosed drug, there are situations in which a significant effect may occur. For example, if a drug has the potential to exhibit an adverse food effect, drug-containing capsules and tablets which exhibit similar in vitro dissolution rates may actually differ with respect to whether an adverse food effect is observed when the dosage forms are orally dosed. In fact, this has been observed for azithromycin, as exemplified in the Examples herein.

For the in vitro dissolution studies disclosed herein, azithromycin was assayed by HPLC, utilizing a 5 micron alumina based hydrocarbonaceous spherical particle chromatographic column (15 cmx0.4 cm), and a 5 micron alumina based hydrocarbonaceous spherical particle precolumn (5 cmx0.4 cm) (both available from ES Industries, Marlton, N.J.). A mobile phase consisting of 71% phosphate buffer/29% acetonitrile (pH 11) was used, with electrochemical detection (e.g. Bioanalytical Systems, West Lafayette, Ind., LC-4B amperometric detector with dual series glassy carbon electrodes).

For in vivo food effect studies, serum azithromycin is assayed using an HPLC assay described by R. M. Shepard et al. (1991) J. Chromatog. Biomed. Appl. 565, 321–337, with amperometric electrochemical detection. Alternatively, any assay method that produces equivalent results, for example, bioassay, can be used.

Tablets according to the invention contain, as necessary ingredients, azithromycin and a disintegrant. Examples of tablet disintegrants are starch, pregelatinized starch, sodium starch glycolate, sodium carboxymethylcellulose, crosslinked sodium carboxymethylcellulose (sodium croscarmellose; crosslinked starch available under the registered trademark Ac-Di-Sol from FMC Corp., Philadelphia, Pa.), clays (e.g. magnesium aluminum silicate), microcrystalline cellulose (of the type available under the registered trademark Avicel from FMC Corp. or the registered trademark Emcocel from Mendell Corp., Carmel, N.Y.), alginates, gums, surfactants, effervescent mixtures, hydrous aluminum silicate, cross-linked polyvinylpyrrolidone (available commercially under the registered trademark PVP-XL from International Specialty Products, Inc.), and others as known in the art. Preferred disintegrants for azithromycin tablets are sodium croscarmellose (Ac-Di-Sol), sodium starch glycolate (available commercially under the registered trademarks Primojel from Avebe (Union, N.J.) or Generichem, (Little Falls, N.J.) and Explotab from Mendell Corp.), microcrystalline cellulose (Avicel), and cross-linked polyvinylpyrrolidone (PVP-XL). Azithromycin tablets of this invention comprise azithromycin and 1–25% disintegrant, preferably 3–15% disintegrant based on total tablet weight. For example, a 463.5 mg tablet (250 mg activity azithromycin) may contain 9 mg sodium croscarmellose and 27 mg pregelatinized starch.

In addition to the active ingredient azithromycin and a disintegrant, tablets according to this invention may be formulated to optionally include a variety of conventional excipients, depending on the exact formulation, such as binders, flavorings, buffers, diluents, colors, lubricants, sweetening agents, thickening agents, and glidants. Some excipients can serve multiple functions, for example as both binder and disintegrant.

Examples of binders are acacia, cellulose derivatives (such as methylcellulose and carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose), gelatin, glucose, dextrose, xylitol, polymethacrylates, polyvinylpyrrolidone, starch paste, sucrose, sorbitol, pregelatinized starch, gum tragacanth,

alginic acids and salts thereof such as sodium alginate, magnesium aluminum silicate, polyethylene glycol, guar gum, bentonites, and the like. A preferred binder for azithromycin tablets is pregelatinized starch (available, for example, under the registered trademark Starch 1500, from Colorcon, Inc., West Point, Pa.).

Flavors incorporated in the composition may be chosen from synthetic flavor oils and flavoring aromatics and/or natural oils, extracts from plants leaves, flowers, fruits, and so forth and combinations thereof. These may include cinnamon oil, oil of wintergreen, peppermint oils, clove oil, bay oil, anise oil, eucalyptus, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, oil of bitter almonds, and cassia oil. Also useful as flavors are vanilla, citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences, including apple, banana, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot, and so forth. The amount of flavoring may depend on a number of factors including the organoleptic effect desired. Generally the flavoring will be present in an amount of from 0.5 to about 3.0 percent by weight based on the total tablet weight, when a flavor is used.

A variety of materials may be used as fillers or diluents. Examples are spray-dried or anhydrous lactose, sucrose, dextrose, mannitol, sorbitol, starch (e.g. starch 1500), cellulose (e.g. microcrystalline cellulose; Avicel), dihydrated or anhydrous dibasic calcium phosphate (available commercially under the registered trademark Emcompress from Mendell or A-Tab and Di-Tab from Rhone-Poulenc, Inc., Monmouth Junction, N.J.), calcium carbonate, calcium sulfate, and others as known in the art.

Lubricants can also be employed herein in the manufacture of certain dosage forms, and will usually be employed when producing tablets. Examples of lubricants are magnesium stearate, stearic acid, glycerylbehapiate, polyethylene glycol, ethylene oxide polymers (for example, available under the registered trademark Carbowax from Union Carbide, Inc., Danbury, Conn.), sodium lauryl sulfate, magnesium lauryl sulfate, sodium oleate, sodium stearyl fumarate, DL-leucine, colloidal silica, and others as known in the art. Preferred lubricants are magnesium stearate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants generally comprise 0.5 to 7.0% of the total tablet weight.

Other excipients such as glidants and coloring agents may also be added to azithromycin tablets. Coloring agents may include titanium dioxide and/or dyes suitable for food such as those known as F. D. & C. dyes and natural coloring agents such as grape skin extract, beet red powder, beta carotene, annato, carmine, turmeric, paprika, and so forth. A coloring agent is an optional ingredient in the compositions of this invention, but when used will generally be present in an amount up to about 3.5 percent based on the total tablet weight.

As known in the art, tablet blends may be dry-granulated or wet granulated before tableting. Alternatively, tablet blends may be directly compressed. The choice of processing approach depends upon the properties of the drug and chosen excipients, for example particle size, blending compatibility, density and flowability. For azithromycin tablets, granulation is preferred, with wet granulation being most preferred. Azithromycin may be wet-granulated, and then other excipients may be added extragranularly. Alternatively, azithromycin and one or more excipients may be wet-granulated. In addition, tablets may also be coated, with a coating that exhibits little or no effect on or interference with tablet dissolution, to assure ease of swallowing or to provide an elegant appearance.

In a preferred embodiment, tablets of this invention are film-coated to provide ease of swallowing and an elegant appearance. Many polymeric film-coating materials are known in the art. A preferred film-coating material is hydroxypropylmethylcellulose (HPMC). HPMC may be obtained commercially, for example from Colorcon Corp., in coating formulations containing excipients which serve as coating aids, under the registered trademark Opadry. Opadry formulations may contain lactose, polydextrose, triacetin, polyethyleneglycol, polysorbate 80, titanium dioxide, and one or more dyes or lakes. Other suitable film-forming polymers also may be used herein, including, hydroxypropylcellulose, and acrylate-methacrylate copolymers.

The tableting process itself is otherwise standard and readily practiced by forming a tablet from a desired blend or mixture of ingredients into the appropriate shape using a conventional tablet press. Tablet formulation and conventional processing techniques have been widely described, for Example in *Pharmaceutical Dosage Forms: Tablets;* Edited By Lieberman, Lachman, and Schwartz; Published by Marcel Dekker, Inc., 2d Edition, Copyright 1989, the text of which is herein incorporated by reference.

The azithromycin dosage forms of this invention also include powders to make oral suspensions, and also the oral suspensions themselves. Generally the powder is a non-caking, free flowing powder which is sold direct to pharmacies or other retail outlets and then made up into the actual suspension by a pharmacist. The oral suspension is thus the actual dosage form ingested by patients. The typical shelf life for a suspension is about five days because azithromycin therapy is generally of five days duration.

Azithromycin suspensions according to the invention contain, as necessary ingredients in addition to azithromycin, one or more thickening agents in a total amount of 0.1 to 2%, and a buffer or pH-altering agent in an amount of 0.1 to 2.5%, with percentages being based on the weight of the dry powder formulation. Dispersing agents may also be used in an amount of from 0.05 to 2%. Preservatives may also be used in an amount from 0.1 to 2%.

Suitable thickening agents function as suspending agents and include, for example, hydrocolloid gums known for such purpose, examples of which include xanthan gum, guar gum, locust bean gum, gum tragacanth, and the like. Alternatively, synthetic suspending agents may be used such as sodium carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose and the like.

Dispersing agents include colloidal silicon dioxide, available from Cabot Corporation, Boston, Mass. under the trade designation Cab-O-Sil.

For the purpose of preparing formulations of a powder for oral suspension, the bitter taste of azithromycin may be masked by including a basic buffer or pH-altering agent which will provide a pH of approximately 10 in the constituted suspension. Maintenance of the pH at around 10 minimizes the quantity of azithromycin in solution, and thus masks the bitter taste of the drug. Many combinations of flavors or flavor systems may be used in addition to mask the bitter taste of azithromycin. Preferred flavors are those which provide a constant flavor for approximately 5 days at the elevated pH of the formulation after constitution. A preferred flavor system consists of spray dried cherry #11929, artificial creme de vanilla #11489, and spray-dried artificial banana #15223 available commercially from Bush Boake Allen, Inc., Chicago, Ill. Artificial sweeteners may also be used.

A powder used to make a suspension herein may also contain conventional optional ingredients such as (1) wetting agents such as sorbitan monolaurate, polysorbate 80, and sodium lauryl sulfate; (2) anti-foaming agents and (3) sweeteners and fillers such as glucose. The powder may also contain a buffer to maintain a high pH upon reconstitution, as discussed above. Suitable buffers and pH-altering agents

include anhydrous tribasic sodium phosphate, anhydrous sodium carbonate, glycine, and the like. Suitable preservatives are well known, for example sodium benzoate and the like. After swallowing, azithromycin from a suspension dissolves quickly.

In the preparation of azithromycin powder for oral suspension formulations, all ingredients may be blended together and deagglomerated, as known in the art. Preferably, azithromycin and flavors are blended, and other ingredients are separately blended. Finally, these two blends are blended and deagglomerated.

Preferred oral suspensions are those which resuspend easily after constitution with aqueous media and which do not cake on storage after constitution. Preferred suspensions contain sucrose NF, when sucrose is used, and anhydrous excipients when available, to assure facile suspension upon constitution. The drug-containing powder is generally reconstituted with water.

Suspensions of this invention exhibit about 90% dissolution of azithromycin in vitro in about 15 minutes. The test can be summarized as follows:

Shake the azithromycin-containing bottle to loosen the powder, and constitute the sample as per label instructions, e.g. as described in Example 12 to provide a 40 mg/ml azithromycin suspension. Shake the bottle vigorously for 2 minutes, then allow the bottle to sit for 30 minutes. Shake again vigorously for 15 seconds. Withdraw 5 ml from the bottle (typically equivalent to 200 mg of azithromycin), taking care to eliminate air bubbles. Carefully dispense the 5 ml aliquot of the azithromycin suspension approximately 10 cm over the surface of the dissolution medium (0.10M sodium phosphate buffer, pH 6.0) in a USP Apparatus 2, with the paddles positioned 2.5 cm from the bottom of the vessels. Begin rotating the paddles at 25 rpm, after the Oral Suspension samples have sunk to the bottom of the vessels. Remove approximately 10 ml from the dissolution vessel at each sampling time, filter, and assay filtrate for azithromycin using the HPLC assay described previously.

An azithromycin unit dose packet dosage form (also referred to herein as a "sachet") consists of a unit packet, designed to be emptied into an aqueous vehicle, for example water or a natural or artificial fruit beverage. The packet contains a blend of azithromycin and excipients which is thus reconstituted. The packet contains, as necessary ingredients, azithromycin and a dispersing agent which makes the sachet powder free flowing, for example colloidal silicon dioxide such as Cab-O-Sil from Cabot. Generally the dispersing agent is present in an amount of about 0.2 to 2.0% by weight based on the weight of the dry sachet as it is to be sold. The dispersing agent also serves as a glidant. The formulation may also optionally contain ingredients including (1) a filler or sweetener (e.g. glucose); (2) a buffer (e.g. sodium phosphate); (3) a wetting agent such as a surfactant, for example sodium lauryl sulfate, and (4) flavors such as any of those enumerated herein, and the like. The powder in the packet flows freely and disperses quickly, essentially immediately upon stirring when reconstituted. Azithromycin unit dose packet dosage forms may be prepared by blending and deagglomerating all ingredients, as known in the art. Preferably, the filler (e.g. sucrose), buffer (e.g. anhydrous tribasic sodium phosphate), and glidant (e.g. colloidal silicon dioxide) are blended and deagglomerated, followed by blending with azithromycin and flavors, followed by deagglomeration. The azithromycin in the packet dissolves quickly when evaluated as follows. The contents of a packet are added to a 250 ml beaker containing 60 ml water treated with the Milli-Q Plus system, Millipore Corp. (>18 megohms resistivity). The contents of the beaker are stirred with a spoon until a homogeneous suspension is obtained (1–2 min.). With the paddles raised, the suspension is poured into the center of a dissolution vessel of a USP-2 dissolution apparatus containing 900 ml 0.1M sodium phosphate buffer, pH 6.0. The paddles are then lowered into the vessel, and rotation is begun at 50 rpm. 10 mL aliquots are removed at each time point, filtered, and filtrates are assayed for azithromycin in solution, using an HPLC assay as described above. Using this method, greater than 90% dissolution of a 1 gm azithromycin packet is observed in less than 5 minutes. The packet thus does not exhibit an adverse food effect.

As stated, the oral azithromycin dosage forms disclosed and described above can be administered to a mammal, including man, in need of such treatment when the mammal has eaten, regardless of how recently and of the nature and quantity of food, without exhibiting an adverse food effect. To this end, and as an additional feature of the invention, this invention provides a therapeutic package suitable for commercial sale, comprising a container, an oral dosage form of azithromycin which does not exhibit an adverse food effect contained therein, and, associated with said package, written (i.e., printed) matter non-limited as to whether the dosage form can be taken with or without food. The written matter is of the type containing information and/or instructions for the physician, pharmacist or patient. The written material can be "non-limited as to whether the dosage form can be taken with or without food" by virtue of including no statement regarding whether or not the dosage form can be taken with or without food, i.e. the statement is silent with regard to food effects. Alternatively, the written material can be non-limited by containing one or more statements affirmatively informing the user (i.e., the patient, pharmacist, or physician) that the said oral dosage form can be taken by or administered to a patient regardless of whether the patient has eaten or otherwise imbibed food (optionally, for example, also stating something like "without regard to type or quantity of food"). The written material can not contain limiting language with respect to food, e.g. "This dosage form can not be taken with food" or "This dosage form may only be given after the patient has fasted" or the like.

The container can be in any conventional shape or form as known in the art which is made of a pharmaceutically acceptable material, for example a paper or cardboard box, a glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual dosages for pressing out of the pack according to a therapeutic schedule. The container employed can depend on the exact dosage form involved, for example a conventional cardboard box would not generally be used to hold a liquid suspension. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

Printed or otherwise written matter is associated with the package in which the azithromycin dosage form is sold. The term "associated with" is intended to include all manners in which written matter, such as instructional or informational materials can be associated with a medicament, as known conventionally in the art. Thus written matter can be associated with the container, for example, by being: written on a label (e.g., the prescription label or a separate label) adhesively affixed to a bottle containing an azithromycin suspension; included inside a container as a written package insert, such as inside a box which contains unit dose packets; applied directly to the container such as being printed on the wall of a box; or attached as by being tied or taped, for example as an instructional card affixed to the neck of a bottle via a string, cord or other line, lanyard or tether type device. The written matter may be printed directly on a unit dose pack or blister pack or blister card. If the written matter affirmatively contains a non-limiting statement, the written

matter may contain other information in addition. An affirmative non-limiting statement may, for example, read like the following exemplary statement:

> This product does not exhibit an adverse food effect and may accordingly be administered to patients whether or not they have eaten and without regard to type or quantity of food.

or something similar, such as "may be taken without regard to food".

The invention will now be illustrated by the following examples which are not to be taken as limiting. In general, the examples demonstrate that (1) azithromycin capsules exhibit an adverse food effect, and that more slowly dissolving capsules exhibit a larger food effect, and (2) azithromycin fast dissolving tablet, powder for oral suspension, and unit dose packet dosage forms do not exhibit an adverse food effect.

EXAMPLE 1

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a capsule dosage form with moderate dissolution rate.

Capsules were prepared which contained 250 mg activity azithromycin. The formula for these capsules is presented in Table I. The dissolution behavior of these capsules was evaluated by the method previously discussed, using rotating paddles, 100 rpm, 900 ml pH 6.0 phosphate buffer at 37 degrees C. The average % azithromycin dissolved at 15 minutes was 25%, and at 30 minutes was 76%.

The effect of feeding on azithromycin bioavailability was determined as follows. Eleven healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast (food and fluid) of 12 hr. The dose was swallowed with 150 ml water, and a further 150 ml water was taken at 1 hr post-dosing. On the other occasion, the subjects consumed a meal consisting of milk, bread and butter, bacon, 2 fried eggs, and coffee. The dose was administered with 150 ml water within 30 minutes of completion of the meal. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, and 24 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition. The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.22, with lower and upper 90% confidence levels of 0.06 and 0.84, respectively.

TABLE I

Formulation of 250 mg Azithromycin Capsules. Prepared in #0 white opaque locking type capsules.

INGREDIENT	MG/CAPSULE
Azithromycin*	263.72
Lactose, anhydrous	149.88
Corn starch, hydrous	47.0
Magnesium stearate/Sodium lauryl sulfate (90/10)	9.40
TOTAL	470.0

*Based on a bulk potency of 94.8%; Non-stoichiometric hydrate.

EXAMPLE 2

This example is comparative and demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a capsule dosage form which dissolved more quickly than the capsules of Example 1.

Azithromycin capsules (250 mg strength) were prepared according to the formula in Table II. Dissolution of azithromycin from these capsules was evaluated as in Example 1. In 15 minutes, 97% of the encapsulated azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from this dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after consumption of a meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two ounces of ham, two pieces of toast with two teaspoons of butter and two pats of jelly, and eight ounces whole-fat milk. The oral doses were administered with 250 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on azithromycin oral bioavailability. The average AUCfed/AUCfasted was 0.80, with lower and upper 90% confidence levels of 0.67 and 0.96, respectively.

TABLE II

Formula for Azithromycin capsules. This formula was prepared as a dry granulation and was loaded into #0 opaque locking capsules.

INGREDIENT	MG/CAPSULE
Azithromycin Dihydrate*	262.05
Lactose, anhydrous	151.55
Corn starch, hydrous	47.00
Magnesium stearate/Sodium lauryl sulfate	9.40
TOTAL	470.00

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.

EXAMPLE 3

This example is comparative and demonstrates the effect of a light breakfast on systemic exposure of azithromycin dosed in a capsule dosage form which dissolves quickly.

Azithromycin capsules (250 mg strength) were prepared according to the formula in Table II. Dissolution of azithromycin from these capsules was evaluated as in Example 1. In 15 minutes, 99% of the encapsulated azithromycin was dissolved.

The effect of a light (Continental) breakfast on azithromycin bioavailability from this dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 1000 mg azithromycin (4×250 mg capsules), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed after consumption of a light breakfast consisting of two rolls with butter and jam and Ca. 300 ml of coffee or tea with milk. The oral doses were administered with 240 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, and 46.5 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the

area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.71, with lower and upper 90% confidence levels of 0.53 and 0.95, respectively.

EXAMPLE 4

This example demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a tablet dosage form which dissolves quickly.

Azithromycin tablets were prepared according to the formula given in Table III. Dissolution evaluation was carried out as in Example 1. At 30 minutes, 100% of the azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from these tablets was determined as follows. Twelve healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg tablets), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast, and on the other occasion the subjects were dosed after consumption of a meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two teaspoons of butter and two pats of jelly, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes, ingested over a twenty minute period. The oral doses were administered with 240 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 0.97, with lower and upper 90% confidence levels of 0.82 and 1.13, respectively.

TABLE III

Formula for azithromycin film coated tablets. This formula was compressed to form a 0.262" × 0.531" modified capsular, upper engraved "Pfizer", lower scored, tablet, and was coated with "pink Opadry".

INGREDIENT	WEIGHT (MG/UNIT)
Azithromycin dihydrate*	262.05
Pregelatinized starch**	27.00
Calcium phosphate dibasic, anhydrous	138.84
Sodium croscarmellose***	9.00
Magnesium stearate/Sodium lauryl sulfate (90/10)	13.11
Pink Opadry II##	18.00

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.
**Starch 1500.
***Ac-Di-Sol.
##Contains lactose, hydroxypropyl methylcellulose, titanium dioxide, triacetin, and D&C Red No. 30 Aluminum Lake.

EXAMPLE 5

This example demonstrates the effect of a Japanese meal on systemic exposure of azithromycin dosed in a tablet dosage form which dissolves quickly.

A tablet dosage form of azithromycin was prepared according to the formula described in Table IV. Dissolution of this dosage form was evaluated as in Example 1. In 15 minutes, 100% of the azithromycin dose was dissolved.

The effect of feeding on azithromycin bioavailability from these tablets was determined as follows. Eight healthy male human volunteers were orally dosed with 500 mg azithromycin (2×250 mg tablets), on each of 2 occasions. On one occasion, the subjects were dosed after a 12 hr fast, and on the other occasion the subjects were dosed 30 minutes after consumption of a Japanese meal consisting of rice, miso soup, fried egg, seaweed, spinach, and pickles. The oral doses were administered with 200 ml water. Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 9, 12, 24, 48, 72, 96, 120, 144, and 168 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.00, with lower and upper 90% confidence levels of 0.87 and 1.15, respectively.

TABLE IV

Azithromycin film-coated tablet formula. Capsular plain white film coated tablets (0.262" × 0.531") were compressed and then coated with "White Opadry" and "Clear Opadry".

INGREDIENT	WEIGHT (MG/TABLET)
Azithromycin dihydrate*	262.05
Pregelatinized starch**	27.00
Calcium phosphate dibasic, anhydrous	138.84
Sodium croscarmellose***	9.00
White Opadry##	12.825
Clear Opadry###	0.675
Magnesium Stearate/ Sodium Lauryl Sulfate (90/10)	13.11

*Equivalent to 250 mg azithromycin, based on a bulk potency of 95.4%.
**Starch 1500.
***Ac-Di-Sol.
##Contains hydroxypropyl methylcellulose, titanium dioxide, polyethyleneglycol, and polysorbate 80.
###Contains hydroxypropyl methylcellulose and polyethyleneglycol.

EXAMPLE 6

This example compares the effects of a high fat breakfast and a low fat breakfast on systemic exposure of azithromycin dosed in a "Powder for Oral Suspension" dosage form.

An azithromycin "Powder for Oral Suspension" was prepared according to the formula in Table V. This formula was designed to wet and disperse quickly when reconstituted with an aqueous vehicle. Dissolution of this suspension was evaluated as described in the "Detailed Description". In 15 minutes 97% of the azithromycin dose dissolved; in 30 minutes 99.6% of the azithromycin dose dissolved.

The effect of a high fat meal and a low fat meal on azithromycin bioavailability from this suspension dosage form was determined as follows. Six healthy male human volunteers were orally dosed with 500 mg azithromycin (12.5 ml of a 40 mg/ml oral suspension), on each of 3 occasions. On one occasion, the subjects were dosed after an overnight fast of 10–12 hr. On another occasion the subjects were dosed after consumption of a high fat meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two pats of butter, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes, ingested over a twenty minute period. On the third occasion, the subjects were dosed after consumption of a low fat meal consisting of one ounce of Cheerios (registered trademark of

General Mills Inc.) cereal and eight ounces of whole milk. The oral doses were administered with 240 ml water (two 60 ml rinses of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 48, 72, and 96 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. For the high fat meal, the average AUCfed/AUCfasted was 1.01, with lower and upper 90% confidence levels of 0.79 and 1.28, respectively. For the low fat meal, the average AUCfed/AUCfasted was 1.04, with lower and upper 90% confidence levels of 0.82 and 1.33, respectively.

TABLE V

Formula for azithromycin "Powder for Oral Suspension". To reconstitute this formulation, 0.52 ml water was added per gm dry formulation.

INGREDIENT	WEIGHT (MG/BOTTLE)
Azithromycin dihydrate*	838.57
Sucrose	15487.74
Sodium phosphate tribasic, anhydrous	70.01
Hydroxypropylcellulose (Klucel-EF)	26.62
Xanthan gum (Keltrol)	26.62
FD&C Red #40	0.67
Spray Dried Cherry #11929	59.94
Art. Creme de Vanilla #11489	133.28
S.D. Art. Banana #15223	99.96
TOTAL	16743.41

*Based on a bulk potency of 95.4%.

EXAMPLE 7

This example demonstrates the effect of a high fat breakfast on systemic exposure of azithromycin dosed in a "Single Dose Packet" (sachet) dosage form.

A "Single Dose Packet" (sachet) dosage form of azithromycin was prepared according to the formula described in Table VI. Dissolution of this dosage form was evaluated as described in the "Detailed Description" above. In 15 minutes, 99% of the azithromycin was dissolved.

The effect of feeding on azithromycin bioavailability from this sachet dosage form was determined as follows. Twelve healthy male human volunteers were orally dosed with 1000 mg azithromycin (1 gm sachet), on each of 2 occasions. On one occasion, the subjects were dosed after an overnight fast of at least 12 hr, and on the other occasion the subjects were dosed after consumption of a high-fat meal consisting of two eggs fried in one tablespoon butter, two strips of bacon, two pieces of toast with two teaspoons of butter and with two pats of jelly, eight ounces whole-fat milk, and 6 ounces hash-brown potatoes. The oral doses were administered with 240 ml water (two 60 ml rinses of the oral syringe plus an additional 120 ml). Blood samples were withdrawn prior to dosing, and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96, and 120 hr post-dosing. Serum azithromycin concentration was determined using a high performance liquid chromatography assay. For each subject under each dosing condition, the area under the drug serum concentration vs. time curve (AUC) was determined for each feeding condition.

The ratio AUCfed/AUCfasted was used as a measure of the effect of food on oral bioavailability. The average AUCfed/AUCfasted was 1.12, with lower and upper 90% confidence levels of 0.99 and 1.27.

TABLE VI

Formula for azithromycin "Unit Dose Packet" dosage form. This blend was prepared, and filled into 3.25" × 4" white paper/aluminum/polyethylene laminate sachets. To reconstitute for dosing, the contents of a sachet is added to 60 ml water, and stirred well.

INGREDIENT	WEIGHT (GM/UNIT)
Azithromycin dihydrate*	1.048
Sucrose	9.707
Sodium phosphate tribasic, anhydrous	0.088
Colloidal silicon dioxide	0.025
Spray Dried art cherry #11929	0.038
Spray Dried art banana #15223	0.064
TOTAL	11.000

*Equivalent to 1 gm azithromycin, based on a bulk potency of 95.4% for azithromycin dihydrate.

EXAMPLE 8

Azithromycin tablets of this invention were prepared at 150, 200, 250, 300, 500, and 600 mg dosage strengths. Tablet cores were prepared by wet granulation of all tablet core ingredients (except magnesium stearate/sodium lauryl sulfate). The dried granules were blended with the lubricant mixture magnesium stearate/sodium lauryl sulfate, followed by tableting on a tablet press. Tablets were coated with an aqueous film coat comprising colored and/or clear Opadry. These tablet formulations do not exhibit an adverse food effect. Tablet formulations were as described in Table VII.

TABLE VII

Examples of azithromycin tablet formulations which do not exhibit a food effect.

Component	WEIGHT (MG/TABLET) 150 MG STRENGTH	200 MG STRENGTH	250 MG STRENGTH	300 MG STRENGTH	500 MG STRENGTH	600 MG STRENGTH
Azithromycin dihydrate*	157.23	209.613	262.05	314.46	524.10	628.93
Pregelatinized starch**	16.20	21.60	27.00	32.40	54.00	64.80
Calcium phosphate dibasic, anhydrous	83.305	111.01	138.84	166.61	277.68	333.21
Sodium croscarmellose#	5.400	7.200	9.00	10.80	18.00	21.60

TABLE VII-continued

Examples of azithromycin tablet formulations which do not exhibit a food effect.

Component	150 MG STRENGTH	200 MG STRENGTH	250 MG STRENGTH	300 MG STRENGTH	500 MG STRENGTH	600 MG STRENGTH
	WEIGHT (MG/TABLET)					
Magnesium stearate/ Sodium lauryl sulfate (90/10)	7.865	10.486	13.11	15.73	26.22	31.46
Opadry@	8.1	10.8	13.5	16.2	27.0	32.4
TOTAL	278.1	370.8	463.5	556.2	927.0	1,112.4

*Based on a theoretical potency of 95.4%.
**Starch 1500.
#e.g. Ac-Di-Sol.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifier, and lakes.

EXAMPLE 9

Additional tablet formulations of azithromycin (250 mg) are prepared which do not exhibit an adverse food effect and are described in Table VIII. The diluent in these formulations (calcium phosphate dibasic, anhydrous) may be substituted by calcium phosphate dibasic dihydrate, microcrystalline cellulose, lactose NF/BP/EP/JP, or other appropriate diluent. The lubricant in these tablets (magnesium stearate/sodium lauryl sulfate, 90/10) may be substituted by magnesium stearate and/or colloidal silica or sodium stearyl fumarate. Magnesium stearate and sodium stearyl fumarate are generally used in amounts constituting 0.5–7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1–1% of the total tablet weight. While considerable latitude in relative excipient ratios is possible, the calcium phosphate/pregelatinized starch ratio should be around 2:1 or greater. The Opadry film coat is not necessary to achieve food-independent drug exposure, but serves to improve ease-of-swallowing and tablet appearance and serves to differentiate strengths. The Opadry coat may comprise between 2–6% of the total tablet weight. Tablets at other potencies may be obtained by maintaining the approximate azithromycin/excipient ratios described in Table VIII, and increasing or decreasing total tablet weight.

TABLE VIII

Examples of azithromycin tablet formulations (250 mg) which do not exhibit an adverse food effect.

COMPONENT	FORMULATION 1	FORMULATION 2	FORMULATION 3
	WEIGHT (MG/TABLET)		
Azithromycin dihydrate	262.05	262.05	262.05
Pregelatinized starch	50.0	13.9	50.0
Calcium phosphate dibasic, anh.	115.84	140.94	104.84
Sodium croscarmellose	9.0	20.0	20.0
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.50	13.50	13.50
TOTAL	463.5	463.5	463.5

@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.

EXAMPLE 10

Further 250 mg azithromycin tablet formulations are prepared which do not exhibit an adverse food effect and are presented in Tables IX and X. In these formulations, maize starch, sodium starch glycolate, and crosslinked polyvinylpyrrolidone serve as disintegrants. Calcium phosphate dibasic, lactose NF/BP/EP, and microcrystalline cellulose serve as diluents.

Magnesium stearate/sodium lauryl sulfate serves as a lubricant. Magnesium stearate/sodium lauryl sulfate may be substituted by magnesium stearate and/or colloidal silica or sodium stearyl fumarate. Magnesium stearate and sodium stearyl fumarate are generally used in amounts constituting 0.5–7% of the total tablet weight. Colloidal silica is generally used in an amount constituting 0.1–1% of the total tablet weight. While considerable latitude in relative excipient ratios is possible, the diluent/disintegrant ratio should be around 2:1 or greater. The Opadry film coat is not necessary to achieve food-independent drug exposure, but serves to improve ease-of-swallowing and tablet appearance. The Opadry coat may comprise between 2–6% of the total tablet weight. Tablets at other potencies are obtained by maintaining the approximate azithromycin/excipient ratios described in Tables IX and X, and increasing or decreasing total tablet weight. These formulas are illustrative, and substitutions of other disintegrants, diluents, and lubricants are possible, as known in the art.

TABLE IX

azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	FORMULATION 4	FORMULATION 5	FORMULATION 6
	WEIGHT (MG/TABLET)		
Azithromycin dihydrate	262.05	262.05	262.05
Maize starch*	13.9	27.0	50.0
Calcium phosphate, dibasic** OR Lactose NF/BP/EP/JP OR Microcrystalline cellulose	151.94	138.84	113.84
Sodium starch glycolate# OR Crosslinked polyvinylpyrrolidone##	9.0	9.0	9.0

TABLE IX-continued

azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 4	FORMULATION 5	FORMULATION 6
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.5	13.5	13.5
TOTAL	463.5	463.5	463.5

†Equivalent to 250 mg azithromycin.
*Also called starch NF or cornstarch
**Either anhydrous or dihydrate
‡e.g. Explotab or Primojel
#e.g. PVP-XL from International Specialty Products Inc.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.

TABLE X

Examples of azithromycin tablet formulations which do not exhibit an adverse food effect.

COMPONENT	WEIGHT (MG/TABLET) FORMULATION 7	FORMULATION 8	FORMULATION 9
Azithromycin dihydrate†	262.05	262.05	262.05
Maize starch*	13.9	27.0	27.0
Calcium phosphate, dibasic** OR Lactose	140.94	144.84	127.84
NHBP/EP/P OR Microcrystalline cellulose			
Sodium starch glycolate‡ OR Crosslinked polyvinylpyrrolidone‡#	20.0	3.0	20.0
Magnesium stearate/sodium lauryl sulfate	13.11	13.11	13.11
Opadry@	13.5	13.5	13.5
TOTAL	463.5	463.5	463.5

*Also called starch NF or cornstarch
**Either anhydrous or dihydrate
‡e.g. Explotab or Primojel
#e.g. PVP-XL from International Specialty Products Inc.
@Hydroxypropylmethylcellulose and appropriate plasticizers, film-coating adjuvants, opacifiers, and lakes.
†Equivalent to 250 mg azithromycin.

EXAMPLE 11

The "Powder for Oral Suspension" formulation described in Table XI was prepared. This formulation does not exhibit an adverse food effect.

TABLE XI

A formulation for azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/GM)
Azithromycin dihydrate	47.97
Sucrose NF	578.71
Sorbitol, crystalline, powder, NF/FCC	280.86
Sodium carbonate, anhydrous, NF	18.84
Sodium benzoate, NF/FCC	4.35
Tragacanth gum powder, NF	14.49
Titanium dioxide USP	14.49
Colloidal silicon dioxide, NF	1.45
Aminoacetic acid (glycine) USP	5.80
Spray-dried Art. Strawberry #22653	15.26
Tropical apple punch #26508	7.63
Spray-dried peppermint stick #15634	0.15
TOTAL	1000.00

EXAMPLE 12

Azithromycin "Powder for Oral Suspension" formulations are prepared as illustrated in Tables XII and XIII. The unit potency of these formulations is 600 mg azithromycin/bottle, and the use potency after constitution with water is 40 mg/ml. To constitute, 0.52 ml water is added per gm of blend. 9 mL. water and 16.74 gm blend produce approximately 20 ml suspension. These formulations include 200 mg Azithromycin/bottle overfill. The listed "flavor system" may be freely substituted with other flavors which provide a pleasant taste and are stable at pH 10 over the shelf-life of the constituted suspension (approximately 5 days). The dye may also be freely substituted. The formulations in this Example are illustrative, and not limiting. These formulations do not exhibit an adverse food effect.

TABLE XII

Examples of formulations of Azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/BOTTLE) FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	838.57	838.57	838.57
Sucrose NF	15487.74	15370.54	15487.74
Sodium phosphate tribasic anhydrous	70.01	70.01	70.01
Hydroxypropyl-cellulose	26.62	26.62	0
Xanthan gum	26.62	26.62	0
Sodium carboxy-methylcellulose	0	0	53.24
Colloidal silicon dioxide	0	16.74	0
Glycine	0	100.46	0
Spray-dried cherry #11928	59.94	59.94	59.94
Art. Creme de Vanilla #11489	133.28	133.28	133.28
Spray-dried Art. Banana #15223	99.96	99.96	99.96
FD&C Red #40	0.67	0.67	0.67
TOTAL	16743.41	16743.41	16743.41

TABLE XIII

Examples of formulations of Azithromycin "Powder for Oral Suspension"

COMPONENT	WEIGHT (MG/BOTTLE) FORMULATION 4	FORMULATION 5	FORMULATION 6
Azithromycin dihydrate	838.57	838.57	838.57
Sorbitol	15138.55	7743.87	7656.37
Sucrose NF	0	7743.87	7656.37
Sodium carbonate, anhydrous, NF	302.00	0	150.00
Sodium phosphate tribasic anhydrous	0	70.01	35.00
Hydroxypropyl-cellulose	0	26.62	17.75
Xanthan gum	0	26.62	17.75
Sodium carboxy-methylcellulose	53.24	0	17.75
Colloidal silicon dioxide	16.74	0	10.00
Glycine	100.46	0	50.00
Spray-dried cherry #11929	59.94	59.94	59.94
Art. Creme de Vanilla #11489	133.28	133.28	133.28
Spray-dried Art. Banana #15223	99.96	99.96	99.96
FD&C Red #40	0.67	0.67	0.67
TOTAL	16743.41	16743.41	16743.41

EXAMPLE 14

The following formulations of unit dose packets of azithromycin are prepared as being exemplary, not limiting, of the invention (Tables XIV and XV). The flavor system for these dosage forms may be freely substituted with any flavor system which provides a pleasant taste when the contents of the packet are reconstituted in water or an aqueous beverage. When constituted in water or an aqueous beverage, these dosage forms do not exhibit an adverse food effect.

TABLE XIV

Examples of unit dose packet formulations.

COMPOSITION	FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	1.048	1.048	1.048
sucrose	9.707	9.707	5.0
sorbitol	0	0	0
sodium phosphate tribasic, anhydrous	0.04	0.2	0.088
sodium carbonate, anhydrous	0	0	0
glycine	0	0	0
colloidal silicon dioxide	0.077	0.22	0.055
Spray-dried art. cherry #11929	0.038	0.038	0.038
Spray dried art. banana #15223	0.064	0.064	0.064

TABLE XV

Examples of unit dose packet formulations.

COMPOSITION	FORMULATION 1	FORMULATION 2	FORMULATION 3
Azithromycin dihydrate	1.048	1.048	1.048
sucrose	0	4.85	4.85
sorbitol	9.707	4.85	4.85
sodium phosphate tribasic, anhydrous	0.088	0.088	0.044
sodium carbonate, anhydrous	0	0	0.022
glycine	0	0	0.022
colloidal silicon dioxide	0.055	0.055	0.055
Spray-dried art. cherry #11929	0.038	0.038	0.038
Spray dried art. banana #15223	0.064	0.064	0.064

What is claimed is:

1. An oral dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

2. A dosage form as defined in claim 1, wherein said mammal is a human.

3. A dosage form as defined in claim 1, further comprising a flavoring agent.

4. An oral dosage form of azithromycin which is in the form of a powder for oral suspension containing anhydrous buffer, which is administrable to a mammal that has eaten, which comprises azithromycin, one or more thickening agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

5. A dosage form as defined in claim 4, wherein said mammal is a human.

6. A dosage form as defined in claim 4, further comprising a flavoring agent.

7. A dosage form as defined in claim 6, wherein said flavoring agent is a flavor system consisting of cherry, vanilla, and banana.

8. A dosage form as defined in claim 4, in the form of a suspension made from said powder.

9. An oral dosage form of azithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has eaten, which

comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dosage form effecting at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

10. A dosage form as defined in claim 9, wherein said mammal is a human.

11. A dosage form as defined in claim 9, further comprising an anhydrous buffer.

12. A dosage form as defined in claim 9, wherein said dispersing agent is colloidal silicon dioxide.

13. A dosage form as defined in claim 9, in the form of a suspension made from said unit dose packet.

14. An oral dosage form of azithromycin which is in the form of a tablet made by wet granulation, which is administrable to a mammal that has eaten, which comprises azithromycin and a disintegrant, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

15. A dosage form as defined in claim 14, wherein said mammal is a human.

16. A dosage form as defined in claim 14, further comprising a flavoring agent.

17. An oral dosage form of azithromycin which is in the form of a powder for oral suspension containing an anhydrous buffer, which is administrable to a mammal that has eaten, which comprises azithromycin, one or more thickening agents, and said anhydrous buffer, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

18. A dosage form as defined in claim 17, wherein said mammal is a human.

19. A dosage form as defined in claim 17, further comprising a flavoring agent.

20. A dosage form as defined in claim 19, wherein said flavoring agent is a flavoring system consisting of cherry, vanilla, and banana.

21. A dosage form as defined in claim 17, in the form of a suspension made from said powder.

22. An oral dosage form of azithromycin which is in the form of a unit dose packet containing a dispersing agent, which is administrable to a mammal that has eaten, which comprises azithromycin and said dispersing agent, and which exhibits no adverse food effect, said dosage form exhibiting a value of $(AUC_{fed})/(AUC_{fst})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75, provided that said dosage form contains less than a taste-masking amount of an alkaline earth metal oxide or hydroxide.

23. A dosage form as defined in claim 22, wherein said mammal is a human.

24. A dosage form as defined in claim 22, further comprising an anhydrous buffer.

25. A dosage form as defined in claim 22, wherein said dispersing agent is colloidal silicon dioxide.

26. A dosage form as defined in claim 22, in the form of a suspension made from said unit dose packet.

27. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
6.0% pregelatinized starch;
30.9% anhydrous dibasic calcium phosphate;
2.0% sodium croscarmellose; and
2.9% lubricant.

28. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
11.1% pregelatinized starch;
25.7% anhydrous dibasic calcium phosphate;
2.0% sodium croscarmellose; and
2.9% lubricant.

29. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
3.1% pregelatinized starch;
31.3% anhydrous dibasic calcium phosphate;
4.4% sodium croscarmellose; and
2.9% lubricant.

30. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
11.1% pregelatinized starch;
23.3% anhydrous dibasic calcium phosphate;
4.4% sodium croscarmellose; and
2.9% lubricant.

31. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
3.1% maize starch;
33.8% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

32. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
30.9% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

33. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
11.1% maize starch;
25.7% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

34. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
3.1% maize starch;
31.3% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

35. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;

32.2% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
0.7% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.5% lubricant.

36. A dosage form as defined in claim 1, comprising:
58.2% azithromycin dihydrate;
6.0% maize starch;
28.4% dibasic calcium phosphate, lactose, or microcrystalline cellulose;
4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and
2.9% lubricant.

37. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
92.5% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylcellulose;
0.2% xanthan gum;
trace coloring; and
1.8% flavoring.

38. A dosage form as defined in claim 4, comprising:
4.8% azithromycin dihydrate;
58.0% sucrose;
29.0% sorbitol;
1.9% anhydrous sodium carbonate;
0.4% sodium benzoate;
1.5% tragacanth gum powder;
1.5% titanium dioxide;
1.15% colloidal silicon dioxide;
0.6% glycine; and
2.3% flavoring.

39. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
91.8% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylcellulose;
0.2% xanthan gum;
0.1% colloidal silicon dioxide;
0.6% glycine;
trace coloring; and
1.8% flavoring.

40. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
92.5% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.3% sodium carboxymethylcellulose;
trace coloring; and
1.8% flavoring.

41. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
90.4% sorbitol;
1.8% anhydrous sodium carbonate;
0.3% sodium carboxymethylcellulose;
0.1% colloidal silicon dioxide;
0.6% glycine;
trace coloring; and
1.8% flavoring.

42. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
46.3% sorbitol;
46.3% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylmethylcellulose;
0.2% xanthan gum; and
trace coloring
1.8% flavoring.

43. A dosage form as defined in claim 4, comprising:
5.0% azithromycin dihydrate;
45.7% sucrose;
45.7% sorbitol;
0.9% anhydrous sodium carbonate;
0.2% anhydrous tribasic sodium phosphate;
0.1% hydroxypropylmethylcellulose;
0.1% xanthan gum;
0.1% sodium carboxymethylcellulose;
0.1% colloidal silicon dioxide;
0.3% glycine;
trace coloring; and
1.8% flavoring.

44. A dosage form as defined in claim 9, comprising:
9.5% azithromycin dihydrate;
88.2% sucrose;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

45. A dosage form as defined in claim 9, comprising:
9.5% azithromycin dihydrate;
88.2% sorbitol;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

46. A dosage form as defined in claim 9, comprising:
9.6% azithromycin dihydrate;
88.9% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% colloidal silicon dioxide; and
0.9% flavoring.

47. A dosage form as defined in claim 9, comprising:
9.3% azithromycin dihydrate;
86.1% sucrose;
1.8% anhydrous tribasic sodium phosphate;
2.0% colloidal silicon dioxide; and
0.9% flavoring.

48. A dosage form as defined in claim 9, comprising:
16.7% azithromycin dihydrate;
79.5% sucrose;
1.4% anhydrous tribasic sodium phosphate;
0.9% colloidal silicon dioxide; and
1.6% flavoring.

49. A dosage form as defined in claim 9, comprising:
9.5% azithromycin dihydrate;
44.1% sucrose;
44.1% sorbitol;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and

0.9% flavoring.

50. A dosage form as defined in claim 9, comprising:

9.5% azithromycin dihydrate;

44.1% sucrose;

44.1% sorbitol;

0.4% anhydrous tribasic sodium phosphate;

0.2% anhydrous sodium carbonate;

0.2% glycine;

0.5% colloidal silicon dioxide; and

0.9% flavoring.

51. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

6.0% pregelatinized starch;

30.9% anhydrous dibasic calcium phosphate;

2.0% sodium croscarmellose; and

2.9% lubricant.

52. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

11.1% pregelatinized starch;

25.7% anhydrous dibasic calcium phosphate;

2.0% sodium croscarmellose; and

2.9% lubricant.

53. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

3.1% pregelatinized starch;

31.3% anhydrous dibasic calcium phosphate;

4.4% sodium croscarmellose; and

2.9% lubricant.

54. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

11.1% pregelatinized starch;

23.3% anhydrous dibasic calcium phosphate;

4.4% sodium croscarmellose; and

2.9% lubricant.

55. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

3.1% maize starch;

33.8% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

56. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

6.0% maize starch;

30.9% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

57. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

11.1% maize starch;

25.7% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

2.0% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

58. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

3.1% maize starch;

31.3% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

59. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

6.0% maize starch;

32.2% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

0.7% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

60. A dosage form as defined in claim 14, comprising:

58.2% azithromycin dihydrate;

6.0% maize starch;

28.4% dibasic calcium phosphate, lactose, or microcrystalline cellulose;

4.4% sodium starch glycolate or crosslinked polyvinylpyrrolidone; and

2.9% lubricant.

61. A dosage form as defined in claim 17, comprising:

5.0% azithromycin dihydrate;

92.5% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.2% hydroxypropylcellulose;

0.2% xanthan gum;

trace coloring; and

1.8% flavoring.

62. A dosage form as defined in claim 17, comprising:

4.8% azithromycin dihydrate;

58.0% sucrose;

29.0% sorbitol;

1.9% anhydrous sodium carbonate;

0.4% sodium benzoate;

1.5% tragacanth gum powder;

1.5% titanium dioxide;

1.15% colloidal silicon dioxide;

0.6% glycine; and

2.3% flavoring.

63. A dosage form as defined in claim 17, comprising:

5.0% azithromycin dihydrate;

91.8% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.2% hydroxypropylcellulose;

0.2% xanthan gum;

0.1% colloidal silicon dioxide;

0.6% glycine;

trace coloring; and

1.8% flavoring.

64. A dosage form as defined in claim 17, comprising:

5.0% azithromycin dihydrate;

92.5% sucrose;

0.4% anhydrous tribasic sodium phosphate;

0.3% sodium carboxymethylcellulose;

trace coloring; and

1.6% flavoring.

65. A dosage form as defined in claim 17, comprising:
5.0% azithromycin dihydrate;
90.4% sorbitol;
1.8% anhydrous sodium carbonate;
0.3% sodium carboxymethylcellulose;
0.1% colloidal silicon dioxide;
0.6% glycine;
trace coloring; and
1.8% flavoring.

66. A dosage form as defined in claim 17, comprising:
5.0% azithromycin dihydrate;
46.3% sorbitol;
46.3% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% hydroxypropylmethylcellulose;
0.2% xanthan gum; and
trace coloring
1.8% flavoring.

67. A dosage form as defined in claim 17, comprising:
5.0% azithromycin dihydrate;
45.7% sucrose;
45.7% sorbitol;
0.9% anhydrous sodium carbonate;
0.2% anhydrous tribasic sodium phosphate;
0.1% hydroxypropylmethylcellulose;
0.1% xanthan gum;
0.1% sodium carboxymethylcellulose;
0.1% colloidal silicon dioxide;
0.3% glycine;
trace coloring; and
1.8% flavoring.

68. A dosage form as defined in claim 22, comprising:
9.5% azithromycin dihydrate;
88.2% sucrose;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

69. A dosage form as defined in claim 22, comprising:
9.5% azithromycin dihydrate;
88.2% sorbitol;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

70. A dosage form as defined in claim 22, comprising:
9.6% azithromycin dihydrate;
88.9% sucrose;
0.4% anhydrous tribasic sodium phosphate;
0.2% colloidal silicon dioxide; and
0.9% flavoring.

71. A dosage form as defined in claim 22, comprising:
9.3% azithromycin dihydrate;
86.1% sucrose;
1.8% anhydrous tribasic sodium phosphate;
2.0% colloidal silicon dioxide; and
0.9% flavoring.

72. A dosage form as defined in claim 22, comprising:
16.7% azithromycin dihydrate;
79.5% sucrose;
1.4% anhydrous tribasic sodium phosphate;
0.9% colloidal silicon dioxide; and
1.6% flavoring.

73. A dosage form as defined in claim 22, comprising:
9.5% azithromycin dihydrate;
44.1% sucrose;
44.1% sorbitol;
0.8% anhydrous tribasic sodium phosphate;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

74. A dosage form as defined in claim 22, comprising:
9.5% azithromycin dihydrate;
44.1% sucrose;
44.1% sorbitol;
0.4% anhydrous tribasic sodium phosphate;
0.2% anhydrous sodium carbonate;
0.2% glycine;
0.5% colloidal silicon dioxide; and
0.9% flavoring.

75. A therapeutic package, comprising
a container,
an oral dosage form of azithromycin which exhibits either or both of:
(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm; and/or
(b) a value of $(AUC_{(t=a)})/(AUC_{(t=\infty)})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75,
and, associated with said package, written matter non-limited as to whether the dosage form can be taken with or without food.

76. A therapeutic package as defined in claim 75, wherein said dosage form is in the form of a tablet.

77. A therapeutic package as defined in claim 75, wherein said dosage form is in the form of a powder for oral suspension.

78. A therapeutic package as defined in claim 77, wherein said dosage form is in the form of a suspension made from said powder.

79. A therapeutic package as defined in claim 75, wherein said dosage form is in the form of a unit dose packet.

80. A therapeutic package as defined in claim 79, wherein said dosage form is in the form of a suspension made from said unit dose packet.

81. A method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin in an oral dosage form which exhibits either or both of:
(a) at least about 90% dissolution of azithromycin within about 30 minutes when an amount of the dosage form equivalent to 200 mg of azithromycin is tested as set forth in USP test <711> in a USP-2 dissolution apparatus under conditions at least as stringent as the following: 900 ml sodium phosphate buffer, pH 6.0, 37° C., with paddles turning at 100 rpm; and/or
(b) a value of $(AUC_{(t=a)})/(AUC_{(t=\infty)})$ of at least 0.80 with a lower 90% confidence limit of at least 0.75.

US006268489B1

(12) **United States Patent**
Allen et al.

(10) **Patent No.: US 6,268,489 B1**
(45) **Date of Patent: Jul. 31, 2001**

(54) **AZITHROMYCIN DIHYDRATE**

(75) Inventors: **Douglas J. M. Allen**, New London; **Kevin M. Nepveux**, Old Saybrook, both of CT (US)

(73) Assignee: **Pfizer Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **07/994,040**

(22) Filed: **Dec. 21, 1992**

Related U.S. Application Data

(63) Continuation of application No. 07/449,961, filed on Dec. 11, 1989, now abandoned.

(30) **Foreign Application Priority Data**

Jul. 9, 1987 (WO) PCT/US87/01612

(51) **Int. Cl.**[7] **C07H 17/08**
(52) **U.S. Cl.** 536/7.4; 536/18.5
(58) **Field of Search** 536/7.4, 18.5

(56) **References Cited**

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4,219,641	*	8/1980	Deposato et al.	536/7.2
4,474,768	*	10/1984	Bright	514/29
4,512,982	*	4/1985	Hauske et al.	536/7.2
4,517,359		5/1985	Kobrehel et al.	536/7.4
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Pelizza et al., Farmaco Ed.Sc., 31, 254–262 (1976).
Allen et al., J. Pharm. Sci., 67, 1087–1093 (1978).

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Primary Examiner –Elli Peselev
(74) *Attorney, Agent, or Firm*—Peter C. Richardson; Gregg C. Benson; Mervin E. Brokke

(57) **ABSTRACT**

Non-hygroscopic, azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin) dihydrate and a process therefor.

3 Claims, No Drawings

B

AZITHROMYCIN DIHYDRATE

This is a continuation of application Ser. No. 07/449,961, filed on Dec. 11, 1989 now abandoned as a request for U.S. examination of International Application No. PCT/US87/01612, filed Jul. 9, 1987.

BACKGROUND OF THE INVENTION

The present invention is directed to a valuable new form of azithromycin (9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A), viz., a non-hygroscopic dihydrate form thereof.

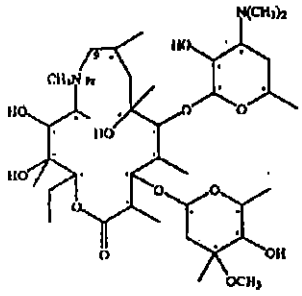
Azithromycin is the U.S.A.N. (generic name) for 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A, a broad spectrum antibacterial compound derived from erythromycin A. Azithromycin was independently discovered by Bright, U.S. Pat. No. 4,474,768 and Kobrehel et al., U.S. Pat. No. 4,517,359. The name "N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A" was employed in these patents. The present more systematic name is based upon the ring expansion and replacement nomenclature of the "IUPAC Nomenclature of Organic Chemistry, 1979 Edition," Pergamon Press, 1979, pp. 68–70, 459, 500–503.

As previously crystallized from ethanol and water (e.g., Example 3 of U.S. Pat. No. 4,474,768), azithromycin was obtained as a hygroscopic monohydrate (for details, see Preparation 1 below). Because of its hygroscopic nature, it is most difficult to prepare and maintain this prior monohydrate product in a form having a constant, reproducible water-content. It is particularly difficult to handle during formulation, since at higher relative humidity levels which are generally required to avoid electrostatic problems (e.g., flow rates, dusting with potential for explosion), the monohydrate readily picks up varying amounts of water, the amount depending upon exposure time and the precise value of the relative humidity (see Preparation 1 below). Such problems have been overcome by the present invention of a stable dihydrate which is essentially non-hygroscopic under conditions of relative humidity conducive to formulation of azithromycin.

SUMMARY OF THE INVENTION

The present invention is directed to a valuable new form of azithromycin, viz., a crystalline, non-hygroscopic dihydrate, prepared by crystallization from tetrahydrofuran and an aliphatic (C_5–C_7)hydrocarbon in the presence of at least two molar equivalents of water.

Azithromycin is of the formula



It is derived from erythromycin A without involvement of asymmetric centers, and so has stereochemistry at each of these centers (*) which is identical with that of erythromycin A. Named systematically as an erythromycin A derivative, the compound is called 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A. Azithromycin, including the present dihydrate, possess broad-spectrum antibacterial activity useful in the treatment of susceptible bacterial infections in mammals, including man.

The expression "aliphatic (C_5–C_7)hydrocarbon" refers to lower boiling hydrocarbon solvents, frequently mixtures of particular boiling point ranges such as those generally referred to as "pentane", "hexane", "hexanes", etc., but which may also be substantially pure, e.g., n-hexane, cyclohexane or methylcyclohexane. A preferred hydrocarbon solvent is so-called "hexane", having a boiling point which ranges near that of pure n-hexane.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is readily carried out. Azithromycin, prepared according to Bright or Kobrehel et al. (cited above) in amorphous form, or as the monohydrate (which may contain, because of its hygroscopicity, more than one molar equivalent of water) is dissolved in tetrahydrofuran. Since the temperatures required for the initial stages of the present process are not critical, ambient temperatures are generally employed, avoiding the cost of heating and cooling. Furthermore, to maximize yield and minimize solvent, labor and equipment costs, the volume of tetrahydrofuran is kept to a near minimum, e.g., 2 liters of solvent per kilogram of substrate. Any insoluble impurities which may be present at this stage are readily removed by conventional methods of filtration. If necessary, the mixture can be decolorized with activated carbon. If desired, the highly concentrated mixture can be diluted with a portion of (C_5–C_7)hydrocarbon prior to filtration, in order to facilitate handling. If the water content of the ingoing bulk is much greater than one molar equivalent, e.g., approaching 2-molar equivalents, it is preferable to dry the mixture for a short period of time over a drying agent such as $MgSO_4$, particularly if hydrocarbon solvent is to be added prior to filtration. To obtain the crystalline dihydrate, water is added to the resulting clear solution, in an amount sufficient to bring the total water content to a level corresponding to at least two molar equivalents, generally not exceeding a level of about 3–4 molar equivalents. The level of water present in the

system is readily monitored by standard Karl Fischer titration. The addition of water is followed by the addition of the hydrocarbon solvent (or of more hydrocarbon solvent, if the mixture was previously diluted before filtration), leading to crystallization of the desired dihydrate product. This stage of the process can be carried out at ambient temperature (e.g. 17–30° C.), but to facilitate the initial crystallization, is preferably carried at slightly elevated temperature (e.g. 30–40° C.). The total volume of hydrocarbon solvent employed is generally at least about four times in volume that of the tetrahydrofuran. Higher volumes of hydrocarbon are satisfactory, but are generally avoided in the interest of minimizing cost. Once crystallization is complete, the product is recovered by filtration, usually after a period of granulation (e.g., 3–24 hours) at ambient temperature. The product is usually vacuum dried of organic solvents (at 20–40° C., conveniently at ambient temperature). To avoid loss of water of hydration, the volatiles and water-content are generally monitored during drying, such that the level of tetrahydrofuran and hydrocarbon will generally fall below 0.25% and the water content will be within 0.3% of theory (4.6%).

Azithromycin dihydrate is formulated and administered in the treatment of susceptible bacterial infections in man according to methods and in amounts previously detailed by Bright, U.S. Pat. No. 4,474,768, cited above and hereby incorporated by reference.

The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the specific details of these examples.

EXAMPLE 1

Non-Hygroscopic Azithromycin Dihydrate

Method A

The hygroscopic monohydrate of Preparation 1 (100 g; water-content:3.1%), tetrahydrofuran (220 ml) and diatomaceous earth (5 g) were combined in a 500 ml Erlenmyer flask, stirred for 30 minutes and filtered with 20 ml of tetrahydrofuran wash. The combined filtrate and wash was transferred to a 3 liter round bottom flask. The solution was stirred vigorously and H_2O (2.0 ml) was added. After 5 minutes, hexane (1800 ml) was added over 5 minutes, with continued vigorous stirring. Following an 18 hour granulation period, title product was recovered by filtration with 1x10 ml hexane wash, and dried in vacuo to 4.6±0.2% H_2O by Karl Fischer, 89.5 g.

Method B

The hygroscopic monohydrate of Preparation 1 (197.6 g) and tetrahydrofuran (430 ml) were charged to a reactor and the mixture stirred to achieve a milky white solution. Activated carbon (10 g) and diatomaceous earth (10 g) were added and the mixture stirred for 15 minutes, then diluted with 800 ml of hexane and filtered with suction over a pad of diatomaceous earth with 250 ml of hexane for wash. The combined filtrate and wash was diluted to 2500 ml with hexane and warmed to 34° C. With stirring, 24.7 ml of H_2O was added. The mixture was allowed to cool to room temperature, granulated for five hours and title product recovered and dried as in Method A, 177.8 g.

The dihydrate melts sharply at 126° C. (hot stage, 10°/minute); differential scanning calorimetry (heating rate, 20° C./minute) shows an endotherm at 127° C.; thermal gravimetric analysis (heating rate 30° C./minute) shows a 1.8% weight loss at 100° C. and a 4.3% weight loss at 150° C.; ir (KBr) 3953, 3553, 3488, 2968, 2930, 2886, 2872, 2827, 2780, 2089, 1722, 1664, 1468, 1426, 1380, 1359, 1344, 1326, 1318, 1282, 1270, 1252, 1187, 1167, 1157, 1123, 1107, 1082, 1050, 1004, 993, 977, 955, 930, 902, 986, 879, 864, 833, 803, 794, 775, 756, 729, 694, 671, 661, 637, 598, 571, 526, 495, 459, 399, 374, 321 and 207 cm^{-1}; [alpha]$^{25}_D$=41.4° (c=1, $CHCl_3$).

Anal. Calcd. for $C_{38}H_{72}N_2O_{12}\cdot 2H_2O$: C, 58.14; H, 9.77; N, 3.57; OCH_3, 3.95; H_2O, 4.59. Found: C, 58.62; H, 9.66; N, 3.56; OCH_3, 4.11; H_2O, 4.49. Neutralization Equivalent (0.5N HCl in 1:1 CH_3CN:H_2O): Calcd.: 374.5. Found: 393.4.

Samples of a dihydrate, slightly over dried to contain 4.1% water (less than theoretical) rapidly picked-up water at 33%, 75% or 100% relative humidities to achieve the theoretical water content (4.6%) for the dihydrate. At 33% and 75% relative humidities, water content remained essentially constant for at least 4 days. At 100% relative humidity, the water content further rose to about 5.2, where it remained essentially constant of the next three days.

A sample of the same dihyrate, maintained at 18% relative humidity gradually lost water. At four days, the water content was 2.5% and at 12 days, 1.1%.

PREPARATION 1

Hygroscopic Azithromycin Monohydrate

Substantially following the methylation procedure of Kobrehel et al., U.S. Pat. No. 4,517,359; and the crystallization procedure of Bright, U.S. Pat. No. 4,474,768; 9-deoxo-9a-aza-9a-homoerythromycin A (previously called 11-aza-10-deoxo-10-dihydroerythromycin A; 100 g, 0.218 mol) was dissolved with stirring in 400 ml $CHCl_3$. Formic acid (98%; 10.4 ml, 0.436 mol) and formaldehyde (37%; 16.4 ml, 0.349 mol) were added over 4–5 minutes, and the mixture heated at reflux for 20 hours. The mixture was cooled to ambient temperature, diluted with 400 ml H_2O and adjusted to pH 10.5 with 50% NaOH. The aqueous layer was separated and extracted 2x100 ml with fresh $CHCl_3$. The organic layers were combined, stripped in vacuo to 350 ml, twice diluted with 450 ml of ethanol and restripped to 350 ml, and finally diluted with 1000 ml H_2O over a 1 hour period, passing for 15 minutes as a slurry began to develop after the addition of about 250 ml of H_2O. Title product was recovered by filtration and dried in air at 50° C. for 24 hours, 85 g; mp 136° C.; differential thermal analysis (heating rate 20° C./minute) shows an endotherm at 142° C.; thermal gravimetric analysis (heating rate 30° C./minute) shows a 2.6% weight loss at 100° C. and a 4.5% weight loss at 150° C.; water content 3.92%; ethanol content 1.09%.

Anal. Calcd. for $C_{38}H_{72}N_2O_{12}$ (corrected for ethanol and water content): C, 58.46; H, 9.78; N, 3.74; Alkoxy, 4.67. Found: C, 58.40; H, 9.29; N, 3.50; Alkoxy, 4.52.

A sample of the monohydrate (having a water content of 3.2%) was maintained at 18% relative humidity for 14 days. The sample lost water over the first 24 hours to yield monohydrate having the theoretical water content (2.35%). The water content then remained substantially constant over 14 days, a value of 2.26% being recorded at 14 days.

At 33% relative humidity the water content of a sample of the same monohydrate rapidly rose to 5.6% where it remained substantially steady for at least three days. Similarly at 75% and 100% relative humidity, the water content rose rapidly, but was now maintained at even higher levels, 6.6% and 7.2%, respectively, for at least 3 days.

What is claimed is:

1. Crystalline azithromycin dihydrate.

2. A method of preparing crystalline azithromycin dihydrate which comprises crystallization of amorphous azithromycin or azithromycin monohydrate from a mixture of tetrahydrofuran and a (C_5–C_7) aliphatic hydrocarbon in the presence of at least 2 molar equivalents of water.

3. A method of claim 2 wherein the hydrocarbon is hexane.

* * * * *

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August 5, 2003

By Hand

Jeffrey B. Kindler, Esq.
Senior Vice President and General Counsel
Pfizer Inc.
235 East 42nd Street
New York, NY 10017-5575

Re: Azithromycin - U.S. Patent Nos. 5,605,889 and 6,268,489

Dear Mr. Kindler:

We represent Teva Pharmaceuticals USA, Inc ("Teva"). We write concerning U.S. Patent Nos. 5,605,889 ("the '889 patent"), entitled "Method of Administering Azithromycin," and 6,268,489 ("the '489 patent"), entitled "Azithromycin Dihydrate," both of which are assigned on their face to Pfizer, Inc.

On December 12, 2002, Teva filed with the FDA Abbreviated New Drug Application ("ANDA") No. 65-153 for 250 mg azithromycin tablets. On November 27, 2002, Teva filed ANDA No. 65-150 for 600 mg azithromycin tablets. Teva expects the FDA to approve these ANDAs in due course.

By filing these ANDAs, Teva has made substantial preparations to make, use, offer to sell, sell, and/or import a generic version of ZITHROMAX®. By filing these ANDAs with the intent to obtain approval to market prior to the expiration of the '489 and '889 patents, Teva has committed a technical act of infringement of these patents. In light of these activities, Teva requests that Pfizer grant a covenant to Teva that Pfizer will not enforce the '889 and '489 patents against Teva for having made, making, using, offering for sale, selling, or importing the azithromycin tablets described in Teva's ANDA Nos. 65-153 and 65-150.

Pfizer has sued Novopharm, Teva's Canadian affiliate on the Canadian equivalent of the '489 patent. Based on the information available to Pfizer as a result of that suit, Teva believes that Pfizer has sufficient information to determine whether it believes Teva's manufacture, use, importation, or sale of the azithromycin products covered by the ANDAs infringe the '889 and/or '489 patents. However, should you require further information, Teva will provide to Pfizer, upon execution of an appropriate confidentiality agreement, information regarding the formulation of the products described in Teva's ANDAs, the bioequivalency data included in the ANDAs, and samples of (i) the products described in the ANDAs, (ii) the raw materials used to make those products, and (iii) azithromycin ethanolate monohydrate, the active ingredient in the products described in the ANDAs.

We are prepared to send Pfizer these materials immediately upon execution of an appropriate confidentiality agreement. For your convenience, we attach a form confidentiality agreement. However, we will disclose these materials under any reasonable terms. If our letter is unsatisfactory, please propose an acceptable alternative.

In view of the urgent need to resolve issues of potential patent infringement prior to Teva's marketing of its azithromycin products, we ask that you respond to this letter within forty five (45) days of receipt. If we do not receive a reply within this time frame, we will take appropriate legal action.

Very truly yours,

Steven J. Lee

cc: Richard Egosi, Esq.

Enclosure

CONFIDENTIALITY AGREEMENT

This Confidentiality Agreement is executed by and between TEVA Pharmaceuticals USA ("Teva"), PFIZER, INC. ("Pfizer"), and Counsel therefore.

RECITALS

WHEREAS, pursuant to § 505(j), Title 21 of the Federal Food, Drug and Cosmetic Act ("the Act"), Teva has filed abbreviated new drug applications, ANDA Nos. 65-153 and 65-150, to obtain approval to engage in the commercial manufacture, use, sale, and importation of azithromycin before the expiration of U.S. Patent Nos. 5,605,889 ("the '889 patent") and 6,268,489 ("the '489 patent").

WHEREAS, Pfizer owns the '889 and '489 patents.

WHEREAS, Pfizer manufactures and markets a pharmaceutical product called Zithromax® (azithromycin) and owns and/or controls certain patent rights, trademarks and know-how relating thereto, including the '889 and '489 patents.

WHEREAS, by letter dated August 5, 2003, Teva offered Pfizer certain confidential information of Teva with respect to ANDA Nos. 65-153 and 65-150 and the product Teva proposes to sell thereunder ("Teva Confidential Information") to allow Pfizer to evaluate whether it believes the commercial manufacture, use, sale, or offer for sale in the United States, or the importation into the United States of the azithromycin products described in its ANDAs will infringe, contribute to or induce the infringement of the '889 and '489 patents.

WHEREAS, Teva will provide Counsel for Pfizer with sufficient of Teva's Confidential Information to permit them to conduct an evaluation under appropriate confidentiality provisions as set forth herein.

NOW THEREFORE, in consideration of the mutual covenants herein contained, the parties mutually agree as follows:

1. Teva shall promptly provide to Counsel for Pfizer a copy of documents sufficient to describe in detail formulation of Teva's proposed azithromycin product, including but not limited to the components of the formulation, the percentage of each component used in the formulation and the process by which Teva prepares the proposed azithromycin product; one (1) 50 tablet sample from each lot of Teva's azithromycin tablets, including 250 mg and 600 mg, including one (1) 50 tablet sample from each lot which was submitted to the FDA, or as to which information was submitted to the FDA in connection with ANDAs 65-153 and 65-150, as well as samples of the raw materials used to make those tablets; and the bioequivalency data included in ANDA Nos. 65-153 and 65-150.

2. Counsel for Pfizer shall use the Teva Confidential Information referenced in Paragraph 1 herein for the sole purpose of evaluating whether it believes the commercial

manufacture, sale, or offer for sale within the United States, or the importation into the United States, of the azithromycin products described in ANDA Nos. 65-153 and 65-150 will infringe, contribute to, or induce the infringement of the '889 and '489 patents. At the conclusion of such evaluation, but in no event later than September 19, 2003, Counsel for Pfizer shall destroy or return all Teva Confidential Information.

3. Counsel for Pfizer may not disclose Teva's confidential information to Pfizer or any other party, except that Counsel for Pfizer may disclose the physical samples to Pfizer employees for the purpose of conducting in vitro tests, and may disclose any of the confidential information, including the physical samples, to independent experts not associated with Pfizer. Such experts must first be identified to Teva, and Teva must have 5 business days within which to object to such experts. Such experts must be made aware of this agreement and must agree to abide by its terms. Counsel for Pfizer agrees to not disclose, communicate or cause to be communicated to any third party, in any manner whatsoever, any and all of the Teva Confidential Information without receiving the prior written consent of Teva to use such Confidential Information. Counsel for Pfizer will not disclose any of Teva's Confidential Information for any reason whatsoever except as set forth above. Samples of Teva's azithromycin and azithromycin products are not yet approved for marketing in the United States, and may not be administered to human patients or subjects.

4. Counsel for Pfizer shall have no obligation to Teva under this Agreement to maintain the confidentiality of information that:

a. can be demonstrated to have been in the public domain prior to execution of this Agreement;

b. can be demonstrated to have been in possession, either through independent development or from another source not under obligation of secrecy to Teva prior to disclosure of Teva's Confidential information under this Agreement; or

c. becomes part of the public domain by publication or otherwise, not due to any unauthorized acts by Counsel for Pfizer.

5. Counsel for Pfizer, and any independent experts retained by them, agree to maintain the confidentiality of all of Teva's Confidential Information received under the terms of this Agreement unless instructed otherwise by Teva in writing.

6. This Agreement constitutes the entire agreement between the parties and supersedes all previous agreements and understandings relating to the subject matter hereof. This Agreement can only be modified by a writing signed by both parties hereto.

7. This Agreement may be executed by facsimile signatures and/or in counterparts and will become effective upon the date execution has been made by the last party whose execution is required, each such counterpart of which shall be an original, but all of which constitute one agreement.

ACCEPTED AND AGREED TO:

PFIZER, INC.
By:
Title: _____
Date: _____

TEVA PHARMACEUTICALS USA, INC.

By: _____
Title: _____
Date: _____

EXHIBIT C

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., Plaintiff, v. PFIZER INC., Defendant.	Civil Action No. 03-CV-7423 (LAP)

ANSWER AND COUNTERCLAIMS OF PFIZER INC.

Defendant Pfizer Inc. ("Pfizer"), through its undersigned counsel, for its answer to the complaint for declaratory judgment ("Complaint") of plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), responds as follows:

1. Pfizer admits the allegations contained in paragraph 1 of the Complaint.

2. Pfizer admits the allegations contained in paragraph 2 of the Complaint.

3. Pfizer admits the allegations contained in paragraph 3 of the Complaint.

4. Pfizer admits the allegations contained in paragraph 4 of the Complaint.

5. Pfizer admits the allegations contained in paragraph 5 of the Complaint.

6. Pfizer admits that this Court has original jurisdiction over matters arising under 35 U.S.C. § 1 et seq., but denies that this Court has jurisdiction over the subject matter of this declaratory judgment action.

7. Pfizer admits that Teva filed this declaratory judgment action for non-infringement and invalidity but denies the remaining allegations contained in paragraph 7 of the Complaint.

8. Pfizer admits the allegations contained in paragraph 8 of the Complaint.

9. Pfizer admits the allegations contained in paragraph 9 of the Complaint.

10. Pfizer admits the allegations contained in paragraph 10 of the Complaint.

11. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 11 of the Complaint.

12. Pfizer admits that *azithromycin* is a component of Pfizer's Zithromax® product, admits that United States Patents Nos. 5,605,889 (the "'889 patent") and 6,268,489 (the "'489 patent") relate to azithromycin, denies that the phrase "contain claims directed to azithromycin" is an accurate description of the claims of the patents, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in paragraph 12 of the Complaint.

13. Pfizer admits that it initiated a proceeding in Canada under Canadian law against the Canadian Minister of Health and Novopharm regarding Novopharm's Notice of Allegation concerning the Canadian counterpart to Pfizer's '489 patent. Pfizer affirmatively states that such proceeding is not an action for patent infringement, and the Canadian proceeding will not conclusively determine questions of patent infringement or invalidity, and Pfizer denies the remaining allegations contained in paragraph 13 of the Complaint.

14. Pfizer admits that, by letter dated August 5, 2003 (a copy of which is attached to as Exhibit C to the Complaint), Teva requested that Pfizer provide a covenant that Pfizer will not enforce the '889 and '489 patents against Teva, Teva requested a response within 45 days of receipt, and, having no obligation, Pfizer did not respond to the August 5, 2003 letter.

15. Pfizer admits that it or its affiliates are parties in the referenced actions and refers to the respective complaints for the complete contents thereof, and denies the remaining allegations contained in paragraph 15 of the Complaint.

16. Pfizer denies the allegations contained in paragraph 16 of the Complaint.

17. Pfizer admits that Teva filed this declaratory judgment action but denies the remaining allegations contained in paragraph 17 of the Complaint.

18. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 18 of the Complaint.

19. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 19 of the Complaint.

20. Pfizer denies the allegations contained in paragraph 20 of the Complaint.

21. Pfizer denies the allegations contained in paragraph 21 of the Complaint.

22. Pfizer denies that Teva is entitled to the relief sought in items A-F in the "Prayer for Relief" of the Complaint.

AFFIRMATIVE DEFENSES TO COMPLAINT

23. The Court lacks subject matter jurisdiction over Teva's declaratory judgment action.

24. Teva's Complaint is barred, in whole or in part, because it fails to state a claim upon which relief may be granted.

PRAYER FOR RELIEF REGARDING COMPLAINT

WHEREFORE, Pfizer respectfully requests that the Court enter an Order and Judgment:

A. Dismissing Teva's Complaint with prejudice;

B. Awarding to Pfizer its costs and attorneys' fees and expenses incurred in

defending against Teva's Complaint; and

C. Awarding Pfizer such other and further relief as the Court deems just and proper.

COUNTERCLAIMS OF PFIZER INC.

In view of this Court's July 27, 2004 decision and accompanying Order, and contingent upon a final determination that this Court has subject matter jurisdiction over Teva's Complaint, defendant Pfizer Inc. ("Pfizer"), through its undersigned counsel, asserts the following compulsory counterclaims ("Counterclaims") against plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"):

THE PARTIES

1. Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, New York, 10017-5575.

2. Upon information and belief, Teva Pharmaceuticals USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090.

JURISDICTION AND VENUE

3. Pfizer's assertion of these Counterclaims is predicated upon this Court's July 27, 2004 decision and accompanying Order. Nothing herein is intended to waive or detract from Pfizer's position that subject matter jurisdiction for the instant action is lacking.

4. To the extent the Court has jurisdiction over Teva's declaratory judgment action, this Court also has subject matter jurisdiction over these Counterclaims pursuant to 28 U.S.C. §§ 1331 and 1338(a).

5. Teva is subject to personal jurisdiction in this judicial district.

6. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Pfizer's Patents

7. On February 25, 1997, the United States Patent and Trademark Office issued United States Patent No. 5,605,889 (the "'889 patent"), entitled "Method of Administering Azithromycin." The '889 patent has been assigned to, and continues to be owned by, Pfizer.

8. On July 31, 2001, the United States Patent and Trademark Office issued United States Patent No. 6,268,489 (the "'489 patent"), entitled "Azithromycin Dihydrate." The '489 patent has been assigned to, and continues to be owned by, Pfizer.

Zithromax®

9. Pfizer holds approved New Drug Applications ("NDAs") for, among other dosage forms, 250 mg and 600 mg *azithromycin* tablets (the "Zithromax® NDAs").

10. Pfizer markets and sells its *azithromycin* products under the trade name Zithromax®.

Teva's ANDAs

11. Teva has represented that it submitted Abbreviated New Drug Application No. 65-153 to the FDA pursuant to 21 U.S.C. §§ 355(j) (the "250 mg ANDA"), seeking approval to market 250 mg *azithromycin* tablets ("Teva's 250 mg Product").

12. Teva has represented that it submitted Abbreviated New Drug Application No. 65-150 to the FDA pursuant to 21 U.S.C. §§ 355(j) (the "600 mg ANDA," and together with the 250 mg ANDA, the "Teva ANDAs"), seeking approval to market 600 mg *azithromycin* tablets ("Teva's 600 mg Product," and together with Teva's 250 mg Product, the "Teva Products").

13. Upon information and belief, the Teva ANDAs refer to and rely upon the Zithromax® NDAs and purport to contain data showing bioequivalence of the Teva Product with

Zithromax®.

14. On or about August 5, 2003, Teva sent to Pfizer a letter stating that Teva had filed the Teva ANDAs and that it was seeking approval to market the Teva Products prior to the expiration of the '889 and '489 patents.

FIRST COUNTERCLAIM – INFRINGEMENT OF U.S. PATENT NO. 5,605,889

15. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-14 of these Counterclaims.

16. Teva has infringed the '889 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting to the FDA ANDA Nos. 65-150 and 65-153, which seek approval from the FDA to engage in the commercial manufacture, use, or sale of Teva's Products prior to the expiration of the '889 patent.

17. Upon information and belief, Teva has knowingly and willfully infringed the '889 patent.

18. Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '889 patent.

SECOND COUNTERCLAIM – INFRINGEMENT OF U.S. PATENT NO. 6,268,489

19. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-14 of these Counterclaims.

20. Teva has infringed the '489 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting to the FDA ANDA Nos. 65-150 and 65-153, which seek approval from the FDA to engage in the commercial manufacture, use, or sale of Teva's Products prior to the expiration of the '489 patent.

21. Upon information and belief, Teva has knowingly and willfully infringed the '489

patent.

22. Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '489 patent.

PRAYER FOR RELIEF REGARDING COUNTERCLAIMS

WHEREFORE, if this Court has subject matter jurisdiction over Teva's Complaint, Pfizer Inc. prays for a judgment in its favor and against Teva Pharmaceuticals USA, Inc., as follows:

A. Entering judgment for Pfizer for infringement of U.S. Patent No. 5,605,889;

B. Entering judgment for Pfizer for infringement of U.S. Patent No. 6,628,489;

C. Entering preliminary and permanent injunctive relief enjoining Teva from making, using, selling, offering to sell, or importing the Teva Products described in ANDA Nos. 65-150 and 65-153 until after the expiration of the '889 patent;

D. Entering preliminary and permanent injunctive relief enjoining Teva from making, using, selling, offering to sell, or importing the Teva Products described in ANDA Nos. 65-150 and 65-153 until after the expiration of the '489 patent;

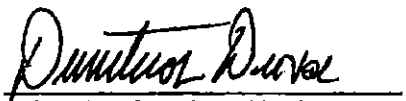
E. Determining that this is an exceptional case under 35 U.S.C. § 285 and awarding Pfizer its reasonable attorneys' fees, costs, and expenses; and

F. Awarding Pfizer such other and further relief as the Court deems just and proper.

Dated: August 23, 2004
New York, New York

Respectfully submitted,

WHITE & CASE LLP

By: 

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Attorneys for Pfizer Inc.

CERTIFICATE OF SERVICE

I hereby certify that on this 23rd day of August, 2004, I caused to be served true and correct copies of the foregoing Answer and Counterclaims of Pfizer Inc. by electronic mail and first-class mail upon counsel for plaintiff Teva Pharmaceuticals USA, Inc. as follows:

Elizabeth J. Holland
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Adam Gahtan

EXHIBIT D

WHITE & CASE LLP
Dimitrios T. Drivas (DD 8891)
Jeffrey J. Oelke (JO 2534)
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1155 Avenue of the Americas
New York, New York 10036
Phone: (212) 819-8200
Attorneys for Defendant Pfizer Inc.

UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC., Plaintiff, v. PFIZER INC., Defendant.	Civil Action No. 04-CV-4979 (LAP)

AMENDED ANSWER AND COUNTERCLAIMS OF PFIZER INC.

Defendant Pfizer Inc. ("Pfizer"), through its undersigned counsel, for its amended answer to the complaint for declaratory judgment ("Complaint") of plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"), responds as follows:

1. Pfizer admits the allegations contained in paragraph 1 of the Complaint.

2. Pfizer admits the allegations contained in paragraph 2 of the Complaint.

3. Pfizer admits the allegations contained in paragraph 3 of the Complaint.

4. Pfizer admits the allegations contained in paragraph 4 of the Complaint.

5. Pfizer admits the allegations contained in paragraph 5 of the Complaint.

6. Pfizer admits that this Court has original jurisdiction over matters arising under 35 U.S.C. § 1 et seq., but denies that this Court has jurisdiction over the subject matter of this declaratory judgment action.

7. Pfizer admits that Teva filed this declaratory judgment action for non-infringement and invalidity but denies the remaining allegations contained in paragraph 7 of the Complaint.

8. Pfizer admits the allegations contained in paragraph 8 of the Complaint.

9. Pfizer admits the allegations contained in paragraph 9 of the Complaint.

10. Pfizer admits the allegations contained in paragraph 10 of the Complaint.

11. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 11 of the Complaint.

12. Pfizer admits that United States Patents Nos. 5,605,889 (the "'889 patent") and 6,268,489 (the "'489 patent") relate to azithromycin, denies that the phrase "contain claims directed to azithromycin" is an accurate description of the claims of the patents, and is without knowledge or information sufficient to form a belief as to the truth of the remaining allegations contained in paragraph 12 of the Complaint.

13. Pfizer admits that it has initiated proceedings in Canada under Canadian law against the Canadian Minister of Health and Novopharm, and other generic companies, regarding Notices of Allegation concerning the Canadian counterparts to Pfizer's '489 and '889 patents. Pfizer affirmatively states that such proceedings are not actions for patent infringement, and the Canadian proceedings will not conclusively determine questions of patent infringement or invalidity, and Pfizer denies the remaining allegations contained in paragraph 13 of the Complaint.

14. Pfizer admits that, by letter dated August 5, 2003 (a copy of which is attached to as Exhibit C to the Complaint), Teva purported to notify Pfizer that it submitted Abbreviated New Drug Applications Nos. 65-150 and 65-153 for generic *azithromycin* tablets to the United States Food and Drug Administration, requested that Pfizer provide a covenant that Pfizer will not enforce the '889 and '489 patents against Teva, and requested a response within 45 days of receipt, and that, having no obligation, Pfizer did not respond to the August 5, 2003 letter.

15. Pfizer admits the allegations contained in paragraph 15 of the Complaint and adds that the instant action is being consolidated with Civil Action No. 03-CV-7423 (LAP).

16. Pfizer admits that it or its affiliates are parties in the referenced actions and refers to the respective complaints for the complete contents thereof, and denies the remaining allegations contained in paragraph 16 of the Complaint.

17. Pfizer denies the allegations contained in paragraph 17 of the Complaint.

18. Pfizer admits that Teva filed this declaratory judgment action but denies the remaining allegations contained in paragraph 18 of the Complaint.

19. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 19 of the Complaint.

20. Pfizer is without knowledge or information sufficient to form a belief as to the truth of the allegations contained in paragraph 20 of the Complaint.

21. Pfizer denies the allegations contained in paragraph 21 of the Complaint.

22. Pfizer denies the allegations contained in paragraph 22 of the Complaint.

23. Pfizer denies that Teva is entitled to the relief sought in items A-F in the "Prayer for Relief" of the Complaint.

AFFIRMATIVE DEFENSES TO COMPLAINT

23. The Court lacks subject matter jurisdiction over Teva's declaratory judgment action.

24. Teva's Complaint is barred, in whole or in part, because it fails to state a claim upon which relief may be granted.

PRAYER FOR RELIEF REGARDING COMPLAINT

WHEREFORE, Pfizer respectfully requests that the Court enter an Order and Judgment:

A. Dismissing Teva's Complaint with prejudice;

B. Awarding to Pfizer its costs and attorneys' fees and expenses incurred in defending against Teva's Complaint; and

C. Awarding Pfizer such other and further relief as the Court deems just and proper.

COUNTERCLAIMS OF PFIZER INC.

In view of this Court's July 27, 2004 decision and accompanying Order, and contingent upon a final determination that this Court has subject matter jurisdiction over Teva's Complaint, defendant Pfizer Inc. ("Pfizer"), through its undersigned counsel, asserts the following compulsory counterclaims ("Counterclaims") against plaintiff Teva Pharmaceuticals USA, Inc. ("Teva"):

THE PARTIES

1. Pfizer Inc. is a corporation organized and existing under the laws of the State of Delaware, having a place of business at 235 East 42nd Street, New York, New York, 10017-5575.

2. Upon information and belief, Teva Pharmaceuticals USA, Inc. is a corporation organized and existing under the laws of the State of Delaware, having its principal place of

business at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090.

JURISDICTION AND VENUE

3. Pfizer's assertion of these Counterclaims is predicated upon this Court's July 27, 2004 decision and accompanying Order. Nothing herein is intended to waive or detract from Pfizer's position that subject matter jurisdiction for the instant action is lacking.

4. To the extent the Court has jurisdiction over Teva's declaratory judgment action, this Court also has subject matter jurisdiction over these Counterclaims pursuant to 28 U.S.C. §§ 1331 and 1338(a).

5. Teva is subject to personal jurisdiction in this judicial district.

6. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400(b).

Pfizer's Patents

7. On February 25, 1997, the United States Patent and Trademark Office issued United States Patent No. 5,605,889 (the "'889 patent"), entitled "Method of Administering Azithromycin." The '889 patent has been assigned to, and continues to be owned by, Pfizer.

8. On July 31, 2001, the United States Patent and Trademark Office issued United States Patent No. 6,268,489 (the "'489 patent"), entitled "Azithromycin Dihydrate." The '489 patent has been assigned to, and continues to be owned by, Pfizer.

Zithromax®

9. Pfizer holds an approved New Drug Application ("NDA") for, among other dosage forms, 500 mg *azithromycin* tablets (the "Zithromax® NDA").

10. Pfizer markets and sells its *azithromycin* products under the trade name Zithromax®.

Teva's ANDA

11. Teva has represented that it submitted Abbreviated New Drug Application No. 65-193 to the FDA pursuant to 21 U.S.C. §§ 355(j) (the "Teva ANDA"), seeking approval to market 500 mg *azithromycin* tablets (the "Teva Product").

12. Upon information and belief, the Teva ANDA refers to and relies upon the Zithromax® NDA and purports to contain data showing bioequivalence of the Teva Product with Zithromax®.

13. On or about August 5, 2003, Teva sent to Pfizer a letter stating that Teva had filed ANDAs with respect to *azithromycin* and that it was seeking approval to market its *azithromycin* products prior to the expiration of the '889 and '489 patents.

FIRST COUNTERCLAIM – INFRINGEMENT OF U.S. PATENT NO. 5,605,889

14. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-13 of these Counterclaims.

15. Teva has infringed the '889 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting to the FDA ANDA No. 65-193, which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Teva's Product prior to the expiration of the '889 patent.

16. Upon information and belief, Teva has knowingly and willfully infringed the '889 patent.

17. Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '889 patent.

SECOND COUNTERCLAIM – INFRINGEMENT OF U.S. PATENT NO. 6,268,489

18. Pfizer hereby realleges and incorporates by reference the allegations of paragraphs 1-13 of these Counterclaims.

19. Teva has infringed the '489 patent, pursuant to 35 U.S.C. § 271(e)(2)(A), by submitting to the FDA ANDA No. 65-193, which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Teva's Product prior to the expiration of the '489 patent.

20. Upon information and belief, Teva has knowingly and willfully infringed the '489 patent.

21. Pfizer will be irreparably harmed if Teva is not enjoined from infringing the '489 patent.

PRAYER FOR RELIEF REGARDING COUNTERCLAIMS

WHEREFORE, if this Court has subject matter jurisdiction over Teva's Complaint, Pfizer Inc. prays for a judgment in its favor and against Teva Pharmaceuticals USA, Inc., as follows:

A. Entering judgment for Pfizer for infringement of U.S. Patent No. 5,605,889;

B. Entering judgment for Pfizer for infringement of U.S. Patent No. 6,628,489;

C. Entering preliminary and permanent injunctive relief enjoining Teva from making, using, selling, offering to sell, or importing the Teva Product described in ANDA No. 65-193 until after the expiration of the '889 patent;

D. Entering preliminary and permanent injunctive relief enjoining Teva from making, using, selling, offering to sell, or importing the Teva Products described in ANDA No. 65-193 until after the expiration of the '489 patent;

E. Determining that this is an exceptional case under 35 U.S.C. § 285 and awarding Pfizer its reasonable attorneys' fees, costs, and expenses; and

F. Awarding Pfizer such other and further relief as the Court deems just and proper.

Dated: August 27, 2004
New York, New York

Respectfully submitted,

WHITE & CASE LLP

By: _____

Dimitrios T. Drivas (DD 8891)
Jeffrey J. Oelke (JO 2534)
Adam Gahtan (AG 8802)
Brendan G. Woodard (BW 6194)
1155 Avenue of the Americas
New York, New York 10036
Phone: (212) 819-8200
Facsimile: (212) 354-8113

Attorneys for Pfizer Inc.

CERTIFICATE OF SERVICE

I hereby certify that on this 27th day of August, 2004, I caused to be served true and correct copies of the foregoing Amended Answer and Counterclaims of Pfizer Inc. by electronic mail and first-class mail upon counsel for plaintiff Teva Pharmaceuticals USA, Inc. as follows:

Elizabeth J. Holland
KENYON & KENYON
One Broadway
New York, New York 10004-1050
Telephone: (212) 425-7200
Facsimile: (212) 425-5288
E-mail: eholland@kenyon.com

Adam Gahtan

EXHIBIT E

Patent Application
Attorney Docket No.PC8618 Reissue

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF:
CURATOLO, ET AL.

APPLICATION NO.: 11/041,194

FILING DATE: January 20, 2005

TITLE: METHOD OF ADMINISTERING AZITHROMYCIN

Examiner: Elli Peselev

Group Art Unit: 1623

Commissioner for Patents
Mail Stop Reissue
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT AND RESPONSE TO OFFICE ACTION

This is in response to the Examiner's Office Action, dated July 18, 2005, for the above referenced patent application. Applicants kindly request entry of the present amendments and consideration of the remarks herein, which are respectfully presented to place the application in condition for allowance.

Please amend the claims in accordance with the claim listing, which begins at page 2 of this paper.

Express Mail No. EV598971111US

92. (Original) A method as defined in claim 83, wherein said dosage form is in the form of a unit dose packet.

93. (Original) A method as defined in claim 92, wherein said dosage form is in the form of a suspension made from said unit dose packet.

Please add new claim.

100. (New) A method as defined in claim 81, wherein said mammal has eaten food of any sort within 30 minutes prior to dosing azithromycin.

Remarks

Entry of the above amendments to the claims and addition of new claim 100 is respectfully requested. A separate paper is attached hereto that details the status of the claims and sets forth the support for the changes to the claims.

I. Background

The Zithromax® 250mg capsule was first approved in the United States and it was the first azithromycin dosage form marketed anywhere in the world. The Food and Drug Administration (FDA) approved the capsule on November 1, 1991, and Pfizer formally launched the product in March of 1992. The capsules were subsequently approved for commercial distribution in a number of countries around the world. All commercially distributed capsules contained azithromycin dihydrate as the specific polymorph of azithromycin.

In early development of Zithromax®, Pfizer scientists conducted a food effect study using the non-stochiometric hydrate form of azithromycin in a standard hard gelatin capsule. It was observed that this capsule dosage form exhibited a significant adverse food effect, i.e., a significant loss in bioavailability when dosed with food. As a result, Phase III studies were conducted with dosing only in the fasted state. The FDA recognized the food effect limitation with language in the package insert directing patients to take capsules "one hour before or two hours after a meal", i.e., on an empty stomach.

In 1992, Pfizer launched tablet and oral suspension formulations of azithromycin dihydrate in Italy, *with the same package insert as the capsules sold in the U.S.* (dosed in fasted state), it being widely believed, at the time, that the food effect was more likely related to the azithromycin drug substance itself, as opposed to a particular dosage form.

In 1993, it was observed that the Zithromax® tablet formulation was superior to the capsule formulation in that the tablet had no appreciable food effect.

On April 29, 1994, a patent application, issuing as the '889 patent, was filed directed to specific oral dosage forms, to a therapeutic package, and to methods of treatment comprising dosing azithromycin in the "fed" state.

The FDA approved the Zithromax® 250mg tablet for U.S. distribution on July 18, 1996, and Pfizer formally launched the tablet in April of 1997. All commercially distributed tablets contained azithromycin dihydrate as the specific polymorph of azithromycin. As part of the original Zithromax® tablet new drug application (NDA), Pfizer demonstrated

bioequivalence between the tablet and the capsule in the fasted state. Pfizer also demonstrated that the tablet had no adverse food effect. As a result, the FDA granted approval for Zithromax® tablets with a labeling statement indicating that the tablets "may be taken with or without food."

II. Discussion

United States Patent 5,605,889 issued February 25, 1997. Based upon Pfizer's launch of tablet and oral suspension formulations of azithromycin dihydrate in Italy (1992), applicants have (a) deleted dosage form claims 1-74 and package claims 75-80 and 94-99 and (b) narrowed the breadth of method of treatment claims 81-93 (see appendix A) pursuant to 35 USC §251.

Independent claim 81 and claims 82-93 dependent therefrom, refer to a method for treating a microbial infection in a mammal which comprises administering, to a mammal that has eaten in need of such treatment, an antimicrobially effective amount of azithromycin.

Support for narrowing the definition of "eaten" can be found in Examples 4-7 of the '889 patent. In each example, azithromycin is dosed to two (2) patient control groups: (a) first group – subjects who were dosed after an overnight fast of 10-12 hours and (b) second group – subjects who were dosed after consumption of either a high fat or low fat meal. There are no examples describing a control group dosing in the fasted state and consuming a meal post-dose. As a result, the '889 disclosure conveys the requisite "blaze marks" directing the skilled artisan to distinguish the narrower definition of "eaten" (patients who eat food of any sort within one hour prior to dosing) over the broader original definition, Purdue Pharma L.P. v. Faulding, Inc., 2000 U.S. App. Lexis 26797 (Fed Cir. 2000).

Pursuant to 37 C.F.R. §1.178(b) applicants apprise the Office that the United States Patent No. 5,605,889 (the '889 patent) was the subject of Civil Action Nos. 03-7423 (IAP) and 04-4979 (IAP), resulting from a complaint filed by Teva Pharmaceuticals USA, Inc. ("Teva"). On December 21, 2004, Pfizer unconditionally agreed not to enforce the '889 patent against Teva or any Teva affiliate, for having made, making, using, offering for sale, selling, or importing the azithromycin tablets as described in Teva's ANDA Nos. 65-150, 65-153 and 65-193.

The Examiner has rejected claims 81-93 and 100, under 35 U.S.C. 251, as being based upon a defective reissue declaration. The Examiner states that the reissue oath/declaration filed with this application is defective because it fails to identify at least one

error which is relied upon to support the reissue application. See 37 CFR 1.175 (a)(1) and MPEP §1414. The declaration states that claims 81-93, as issued, are described in the prior art, however, said prior art has not been identified and no reason is provided for the cancellation of all the other claims.

Applicants respectfully submit that the filing of a new declaration, herewith, identifying the prior art as the Zithromax (Trademark of Pfizer Inc.) Tablet and Powder for Oral Suspension Package Insert for azithromycin tablets and powder for oral suspension dosage forms sold commercially in Italy (1992).

The Examiner further states that the reissue oath/declaration filed with this application is defective because it fails to contain a statement that all errors which are being corrected in the reissue application up to the time of filing of the oath/declaration arose without any deceptive intention on the part of the applicant (see 37 CFR 1.175 and MPEP§ 1414).

Applicants respectfully submit on page 2 of the declaration a statement that: "All errors corrected in this reissue application arose without any deceptive intention on the part of the application."

Lastly, applicants file herewith a Supplemental Information Disclosure Statement pursuant to 37 CFR 1.56.

Applicants believe that, in view of the amendments and remarks made above, this application is in condition for allowance.

Date: August 25, 2005

B. Timothy Creagan
Attorney for Applicant(s)
Reg. No. 39,156

Pfizer Inc
Patent Department
Eastern Point Road, MS8260-1611
Groton, Connecticut 06340
(860) 715-4546

Status of claims and Support for Claim Changes

Claim Number(s)	Status of Claim	Support for Claim Changes
1-80	Cancelled	
81	Pending (Amended)	Column 3, lines 3-6; and Examples 4-7
82	Pending	
83	Pending	
84	Pending	
85	Pending	
86	Pending	
87	Pending	
88	Pending	
89	Pending	
90	Pending (Amended)	Original claim; correction of dependency
91	Pending	
92	Pending	
93	Pending	
94-99	Cancelled	
100	New	Example 5, particularly, column 14, lines 4-8

EXHIBIT F

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC. Plaintiff, v. PFIZER, INC., Defendant.	03 Civ. 7423(LAP) & 04 Civ. 4979 (LAP) MEMORANDUM AND ORDER

LORETTA A. PRESKA, United States District Judge:

In light of Pfizer's granting to Teva a covenant not to sue with respect to the '489 patent, the parties' motions for discovery and summary judgment (docket nos. 35 and 37) are denied as moot.

The parties shall confer and inform the court of the proposed briefing schedule on Teva's motion for attorney's fees. To the extent that Teva wishes to brief the unenforceability issue in connection with its attorney's fees motion, it may do so by reference to arguments made in papers submitted on the summary judgment motions. Pfizer may respond in like fashion in its opposition papers.

SO ORDERED

February 17, 2006

Loretta A. Preska, U.S.D.J.

EXHIBIT G

IN THE UNITED STATES DISTRICT COURT 06 CV 1134
FOR THE SOUTHERN DISTRICT OF NEW YORK

TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD. Plaintiffs, v. PFIZER INC., Defendant.	**Civil Action No.**

COMPLAINT FOR DECLARATORY JUDGMENT

Plaintiffs Teva Pharmaceuticals USA, Inc. ("Teva USA") and Teva Pharmaceutical Industries Ltd. ("Teva Ltd."), for their Complaint against Pfizer Inc. ("Pfizer"), allege on personal belief as to themselves and on information and belief as to the conduct of Pfizer as follows:

THE PARTIES

1. Teva USA is a Delaware corporation with its principal place of business located at 1090 Horsham Road, North Wales, Pennsylvania, 19454-1090.

2. Teva Ltd. is a corporation organized under the laws of Israel, and maintains its principal place of business at 5 Basel Street, Petach Tikva 49131, Israel.

3. On information and belief, Pfizer is a Delaware corporation with its principal place of business at 235 East 42nd Street, New York, New York, 10017-5575.

4. On information and belief, Pfizer owns U.S. Patent No. 6,977,243 ("the '243 patent"), entitled "Crystal Forms of Azithromycin," a copy of which is attached hereto as Exhibit A.

5. On information and belief, Pfizer holds New Drug Application ("NDA") No. 50-711 for ZITHROMAX® 250 mg azithromycin tablets, NDA No. 50-730 for ZITHROMAX® 600 mg azithromycin tablets; and NDA No. 50-784 for ZITHROMAX® 500 mg azithromycin tablets.

JURISDICTION AND VENUE

6. This Court has original jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a), in that it involves substantial claims arising under the United States Patent Act, 35 U.S.C. § 1 *et seq.*

7. This Court may declare the rights and other legal relations of the parties pursuant to 28 U.S.C. §§ 2201 and 2202 because this is a case of actual controversy within the Court's jurisdiction seeking a declaratory judgment that the '243 patent is invalid and not infringed.

8. Personal jurisdiction exists over the defendant because defendant has its principal place of business within this district, and because defendant does business within this district.

9. Venue is proper in this district under 28 U.S.C. §§ 1391(b) and 1400(b).

THE PRESENCE OF AN ACTUAL CONTROVERSY

10. Teva USA holds Abbreviated New Drug Application ("ANDA") Number 65-153 for 250 mg azithromycin tablets; ANDA Number 65-150 for 600 mg azithromycin tablets and ANDA No. 65-193 for 500 mg azithromycin tablets.

11. On November 14, 2005, the United States Food and Drug Administration ("FDA") granted Teva USA approval to market 250 mg, 500 mg, and 600 mg azithromycin tablets pursuant to its ANDAs. Teva USA began marketing its 250 mg, 500 mg, and 600 mg azithromycin tablets on or about that date.

12. The active pharmaceutical ingredient ("API") in Teva USA's azithromycin tablets is azithromycin monohydrate hemiethanolate (the "hemiethanolate"). The hemiethanolate is a unique crystalline form of azithromycin, which has been patented by Teva Ltd.

13. Pfizer's '243 patent contains claims to azithromycin sesquihydrate (the "sesquihydrate"), which is a crystalline form of azithromycin different from the hemiethanolate.

14. Pfizer has demonstrated its intention to enforce the '243 patent against Teva USA and Teva Ltd. In particular, notwithstanding the fact that the API in Teva USA's azithromycin tablets is not the sesquihydrate, Pfizer has brought suit against Teva USA and Teva Ltd. in the District of Delaware claiming that Teva USA has been and is infringing the '243 patent by importing into the United States and selling and offering to sell within the United States its azithromycin tablets and that Teva Ltd. has actively induced Teva USA to infringe the '243 patent.

15. Pfizer has previously claimed that Teva USA's azithromycin tablets infringe one of its patents. In *Teva Pharmaceuticals USA, Inc. v. Pfizer, Inc.*, 03cv7423 and 04cv4979 (LAP) (consolidated), currently pending before this Court, Teva USA seeks a declaratory judgment that its azithromycin tablets do not infringe Pfizer's U.S. Patent No. 6,268,489 (the "'489 patent"), and that the '489 patent is invalid and unenforceable. The '489 patent claims "crystalline azithromycin dihydrate" ("dihydrate"), another crystalline form of azithromycin different from the hemiethanolate. Pfizer counterclaimed against Teva USA, alleging that Teva USA's sale of its azithromycin tablets would infringe the '489 patent.

16. Pfizer (or its predecessor) has also demonstrated its intention to protect other products from generic competition by Teva USA. On at least five occasions, Pfizer sued or maintained suit against Teva USA (or its related entities) for patent infringement relating to other drugs for which Teva USA has filed an ANDA: (i) *Pfizer Inc. and Pfizer Technologies Ltd. v. Novopharm Ltd.*, 00-cv-01475 (N.D. Ill.), concerning fluconazole; (ii) *Pfizer Inc./Warner-Lambert v. Teva*, 00-cv-4589 and 00-cv-4168 (D.N.J.), concerning gabapentin; (iii) *Schwarz Pharma, Inc., Schwarz Pharma AG and Warner-Lambert Co. v. Teva Pharmaceuticals USA, Inc.*, 01-cv-4995 (D.N.J.), concerning moexipril; (iv) *Bayer and Pfizer v. Biovail & Teva*, 01-cv-1205 and 01-cv-1206 (D.P.R.), concerning nifedipine; and (v) *Warner-Lambert v. Teva USA*, 99-cv-0922 (D.N.J.), concerning quinipril.

17. Based on the above, an actual controversy exists between Teva USA, Teva Ltd. and Pfizer with respect to the '243 patent and Teva USA's 250 mg, 500 mg and 600 mg azithromycin tablets.

COUNT I
DECLARATORY JUDGMENT OF NONINFRINGEMENT

18. The allegations of Paragraphs 1 to 17 are incorporated by reference as if fully set forth herein.

19. Teva USA's manufacture, use, offer for sale, sale, and/or importation of its 250 mg, 500 mg and 600 mg azithromycin tablets pursuant to ANDA Nos. 65-153, 65-193 and 65-150, respectively, has not infringed and does not infringe any valid and properly construed claim of the '243 patent.

COUNT II
DECLARATORY JUDGMENT OF NONINFRINGEMENT

20. The allegations of Paragraphs 1 to 19 are incorporated by reference as if fully set forth herein.

21. Teva Ltd. has not and is not actively inducing Teva USA to infringe any valid and properly construed claim of the '243 patent.

COUNT II
DECLARATORY JUDGMENT OF PATENT INVALIDITY

22. The allegations of Paragraphs 1 to 21 are incorporated by reference as if fully set forth herein.

23. The claims of the '243 patent are invalid for failure to comply with one or more sections of Title 35 U.S.C., including, but not limited to, sections 101, 102, 103, and 112.

PRAYER FOR RELIEF

WHEREFORE, Teva USA and Teva Ltd. respectfully request the Court enter judgment against Pfizer to include:

A. A declaration that Teva USA's manufacture, use, importation, offer for sale or sale of Teva's azithromycin products pursuant to ANDA Nos. 65-153, 65-150, and 65-193 has not infringed and does not infringe any claim of United States Patent No. 6,977,243;

B. A declaration that Teva Ltd. has not directly or indirectly infringed, and is not directly or indirectly infringing, any claim of United States Patent No. 6,977,243;

C. A declaration that United States Patent No. 6,977,243 is invalid;

D. An award to Teva USA and Teva Ltd. of their reasonable costs and attorneys' fees in connection with this action;

E. An injunction prohibiting Pfizer and its officers, agents, employees, representatives, counsel and all persons in active concert or participation with any of them, directly or indirectly, from threatening or charging infringement of, or instituting or maintaining any action for infringement of U.S. Pat. No. 6,977,243 against Teva USA or Teva Ltd., and

F. Such other and further relief as the Court may deem just and proper.

Respectfully submitted,

KENYON & KENYON LLP

Dated: February 14, 2006 By: _____

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Elizabeth J. Holland (EH0850)
Sheila Mortazavi (SM3665)
Cynthia Lambert Hardman (CH2281)
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Fax: (212) 425-5288
Counsel for Plaintiffs, TEVA PHARMACEUTICALS USA, INC. and TEVA PHARMACEUTICAL INDUSTRIES LTD.

EXHIBIT A

US006977243B2

(12) **United States Patent**
Li et al.

(10) **Patent No.: US 6,977,243 B2**
(45) **Date of Patent: *Dec. 20, 2005**

(54) **CRYSTAL FORMS OF AZITHROMYCIN**

(75) Inventors: **Zheng J. Li**, Quaker Hill, CT (US); **Andrew V. Trask**, Stonington, CT (US)

(73) Assignee: **Pfizer Inc.**, New York, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **10/152,106**

(22) Filed: **May 21, 2002**

(65) **Prior Publication Data**

US 2003/0162730 A1 Aug. 28, 2003

Related U.S. Application Data

(60) Provisional application No. 60/292,565, filed on May 22, 2001, provisional application No. 60/297,741, filed on Jun. 12, 2001, and provisional application No. 60/343,041, filed on Dec. 21, 2001.

(51) **Int. Cl.**[7] **A61K 31/70; C07H 17/08**

(52) **U.S. Cl.** **514/29; 536/7.4**

(58) **Field of Search** 514/29; 536/7.4

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WO	WO 0032203	6/2000	A61K/31/70
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WO	WO 0149697	7/2001	C07H/1/00
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WO	WO 03032922	4/2003	

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Primary Examiner—Elli Peselev
(74) *Attorney, Agent, or Firm*—Gregg C. Benson; B. Timothy Creagan; Lance Y. Liu

(57) **ABSTRACT**

The invention relates to crystal forms of azithromycin, an antibiotic useful in the treatment of infections.

24 Claims, 33 Drawing Sheets

FIG. 1

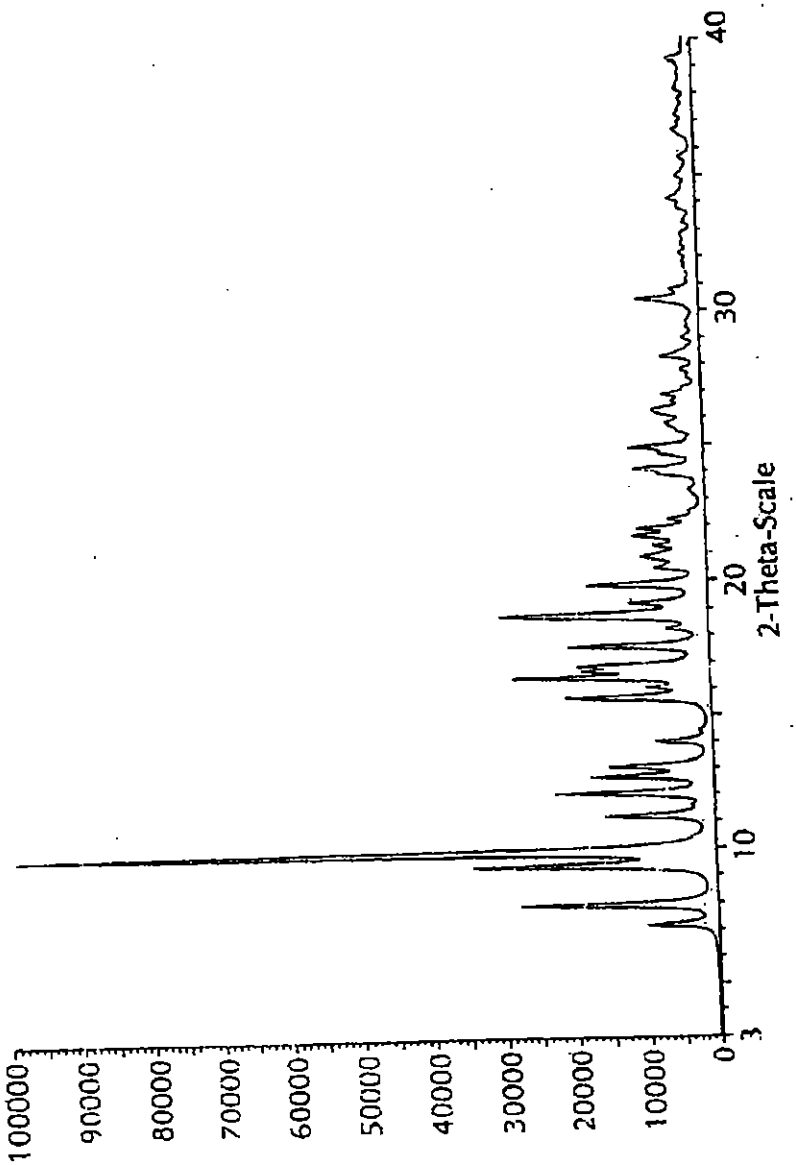
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FIG. 2

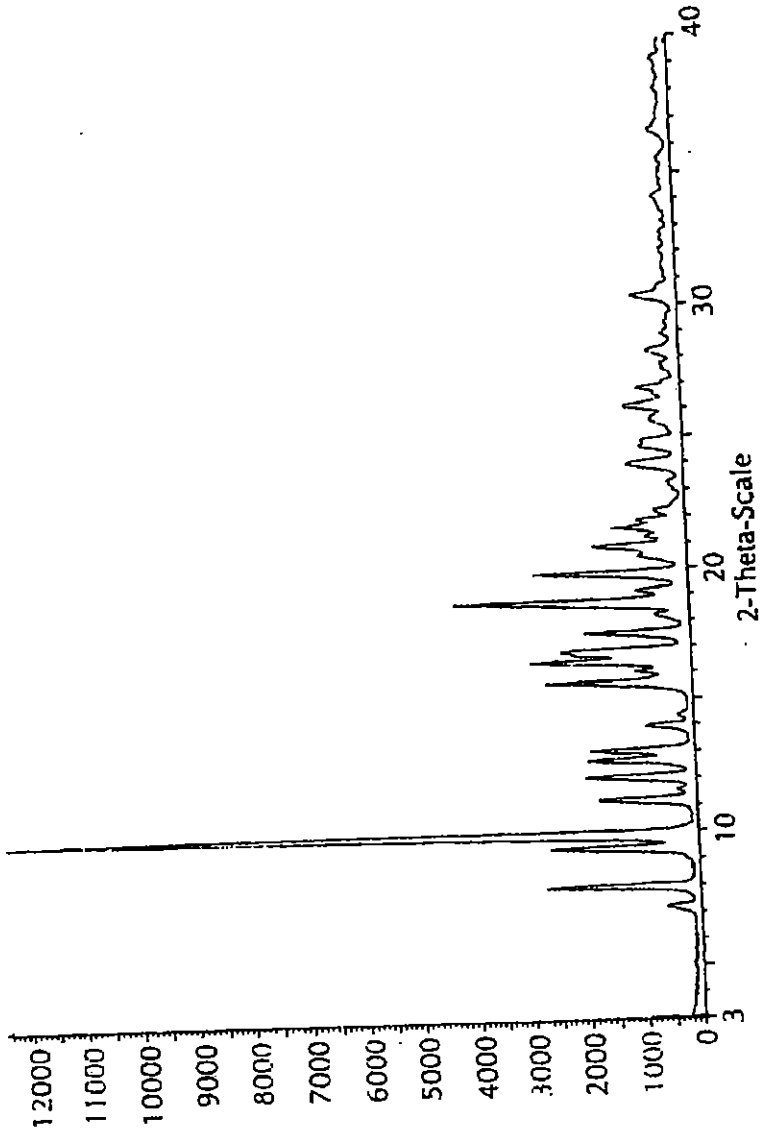
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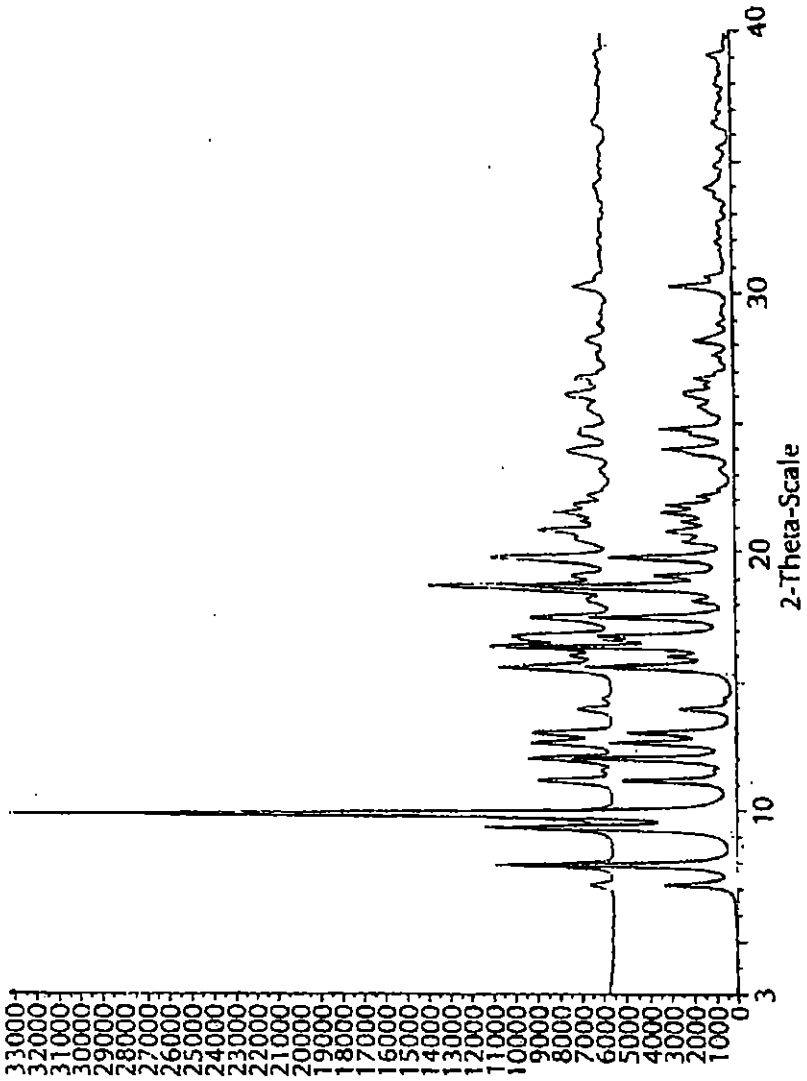
FIG. 3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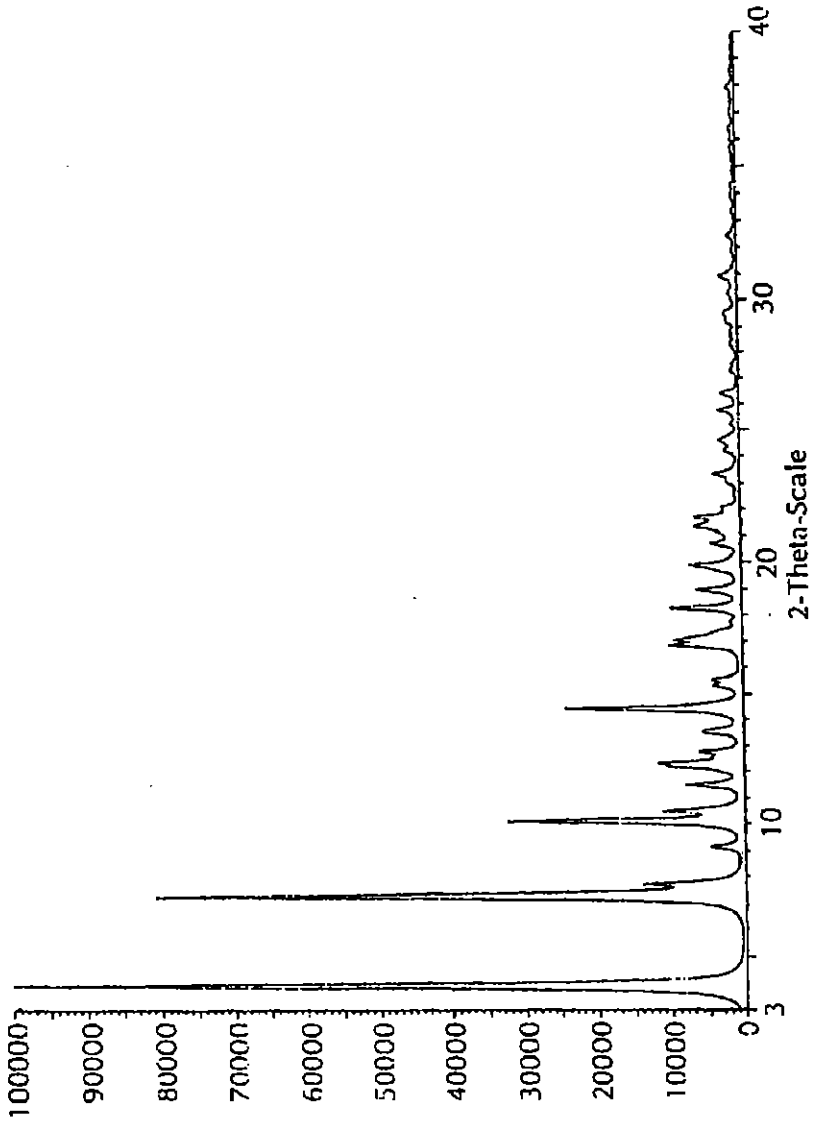
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FIG. 5

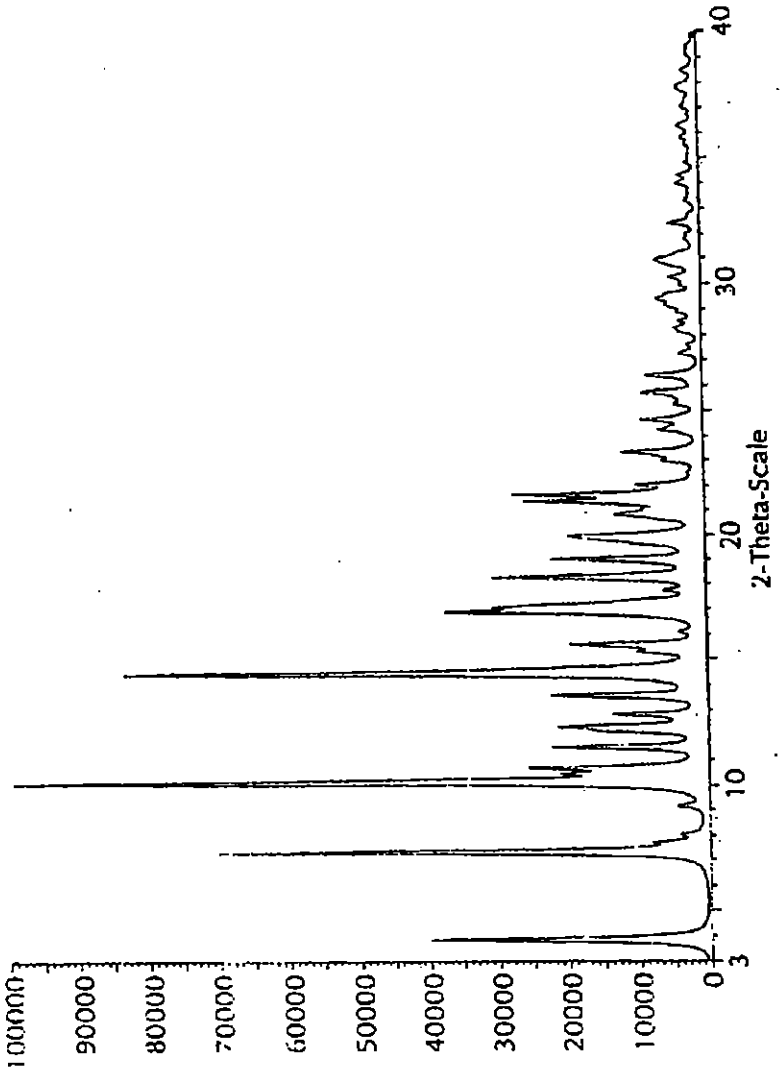
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FIG. 6

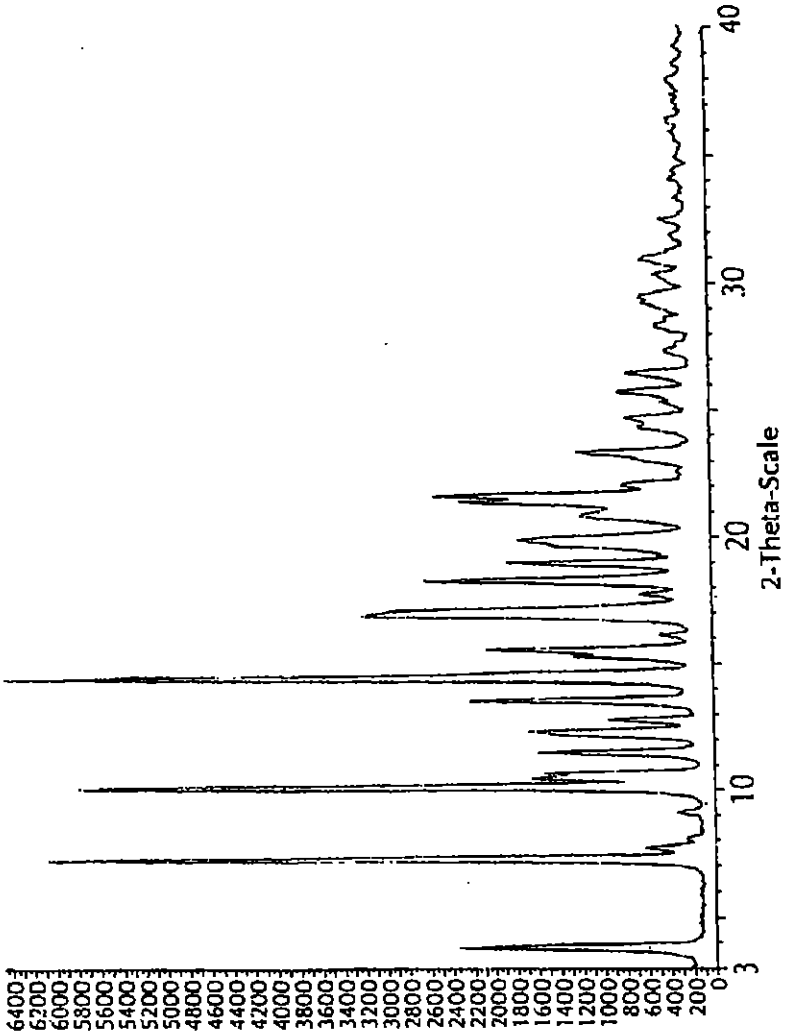
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FIG. 7

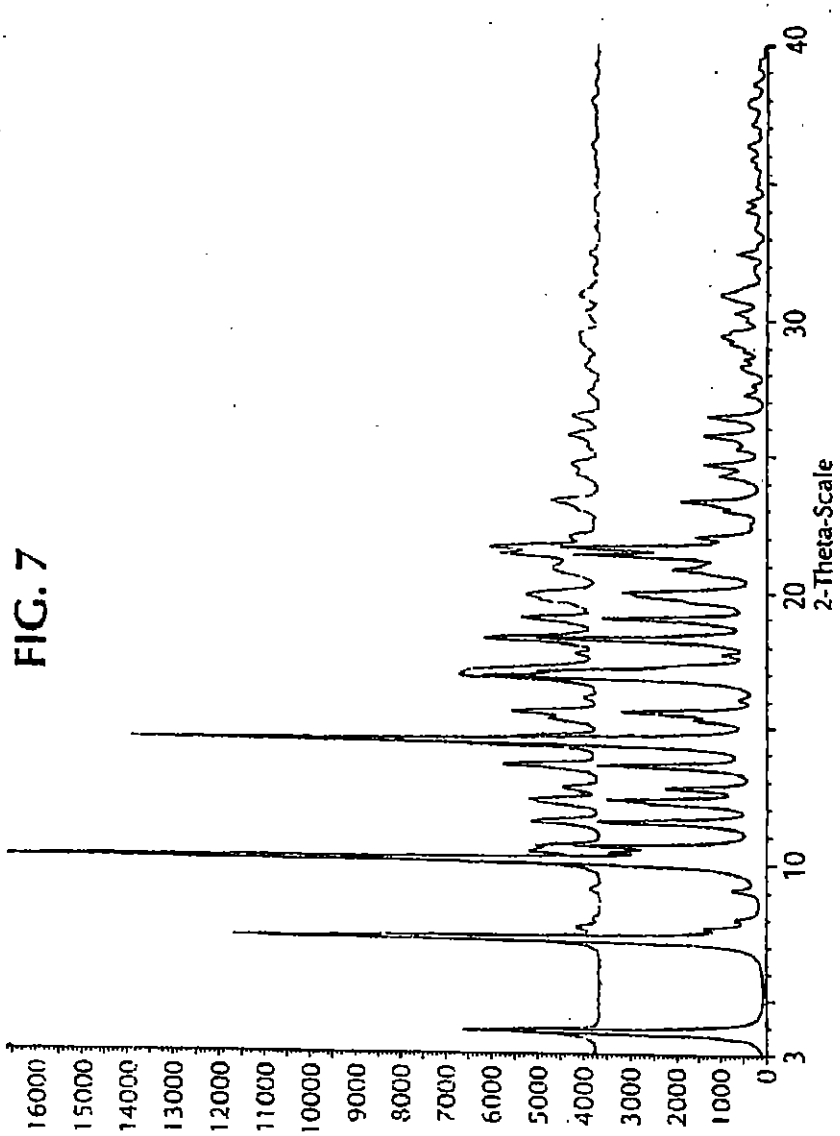
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FIG. 8

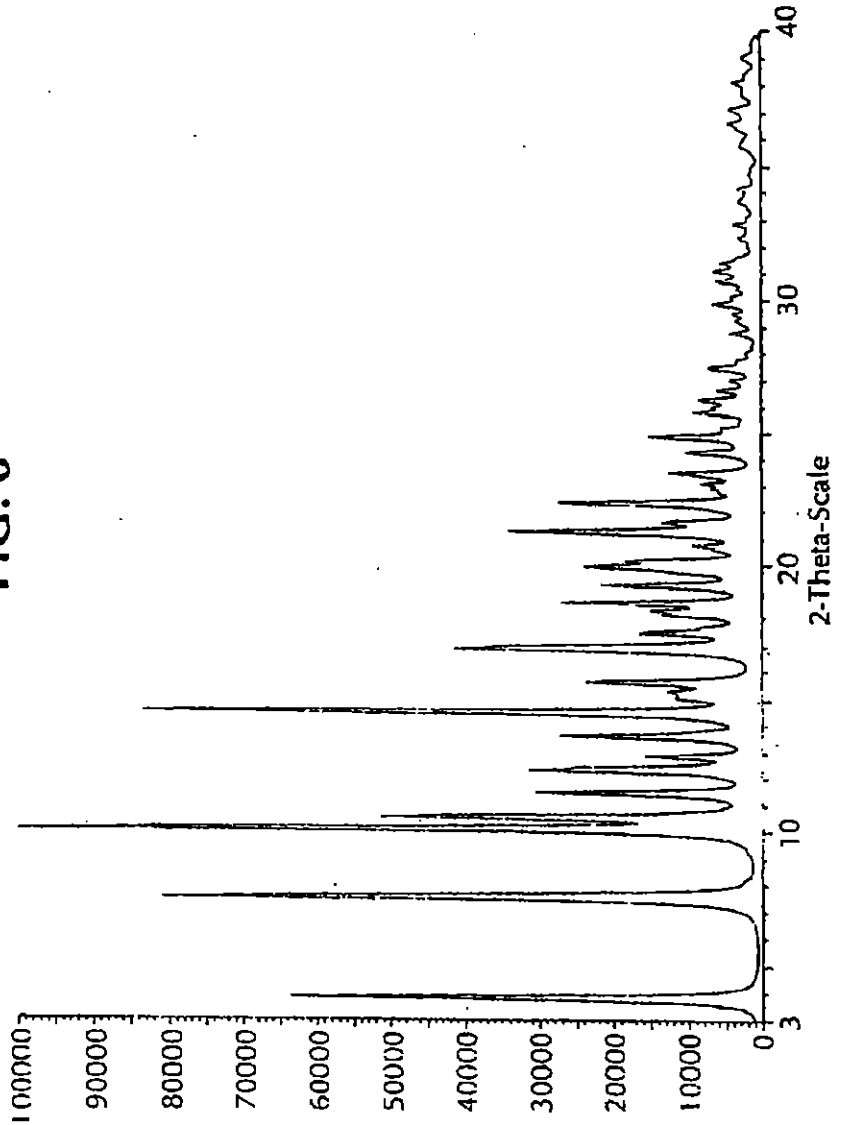
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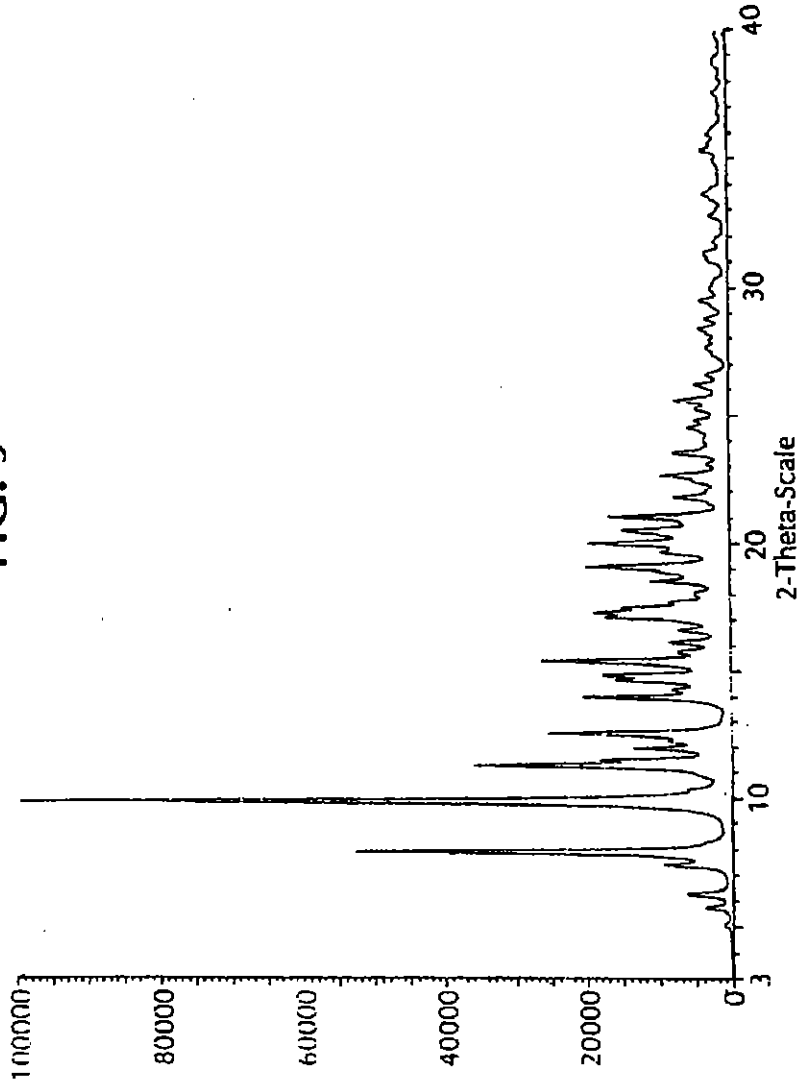
FIG. 9



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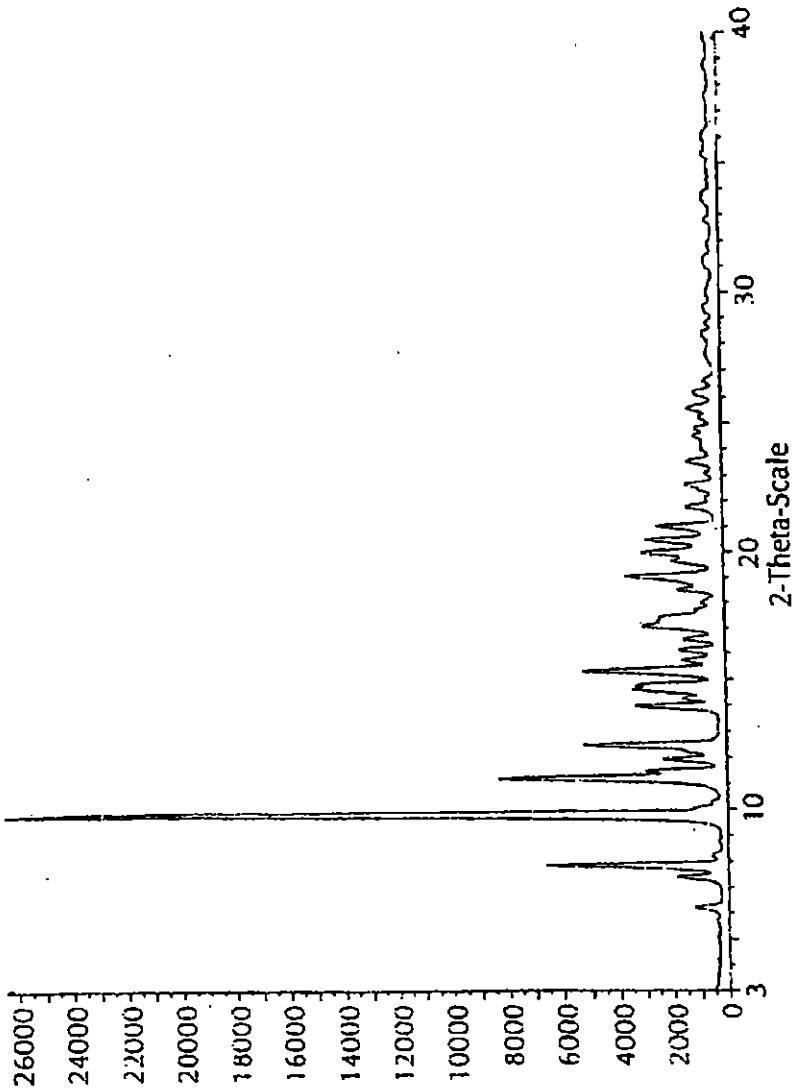
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FIG. 11

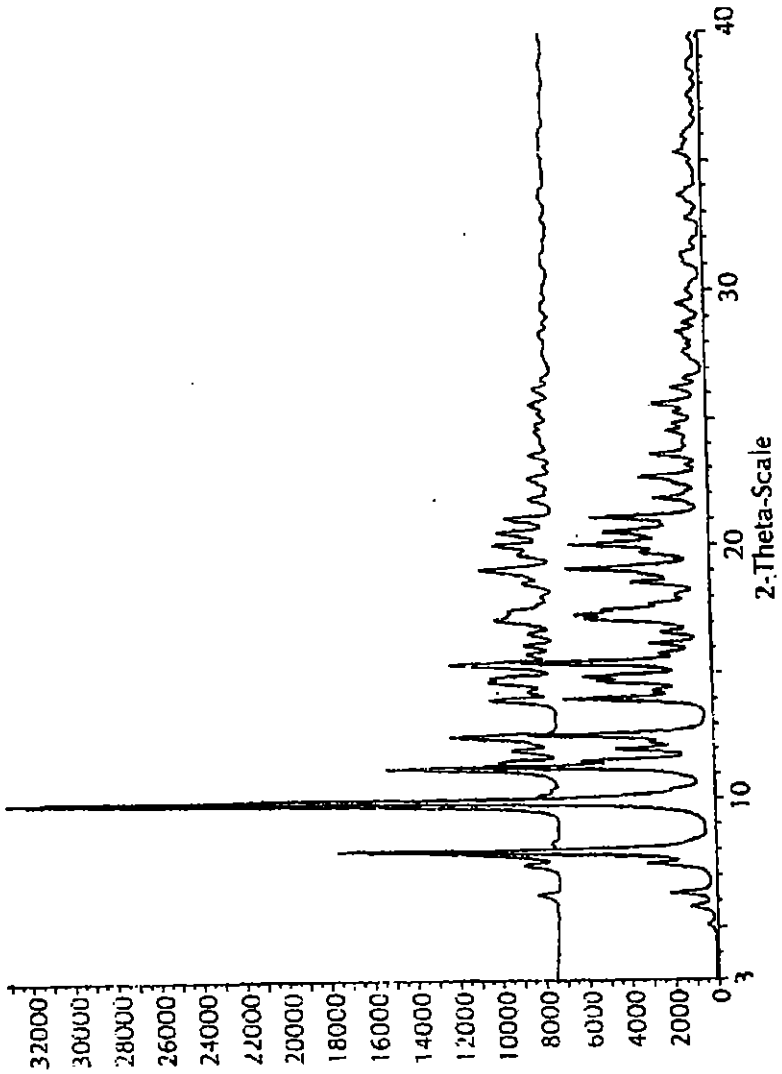
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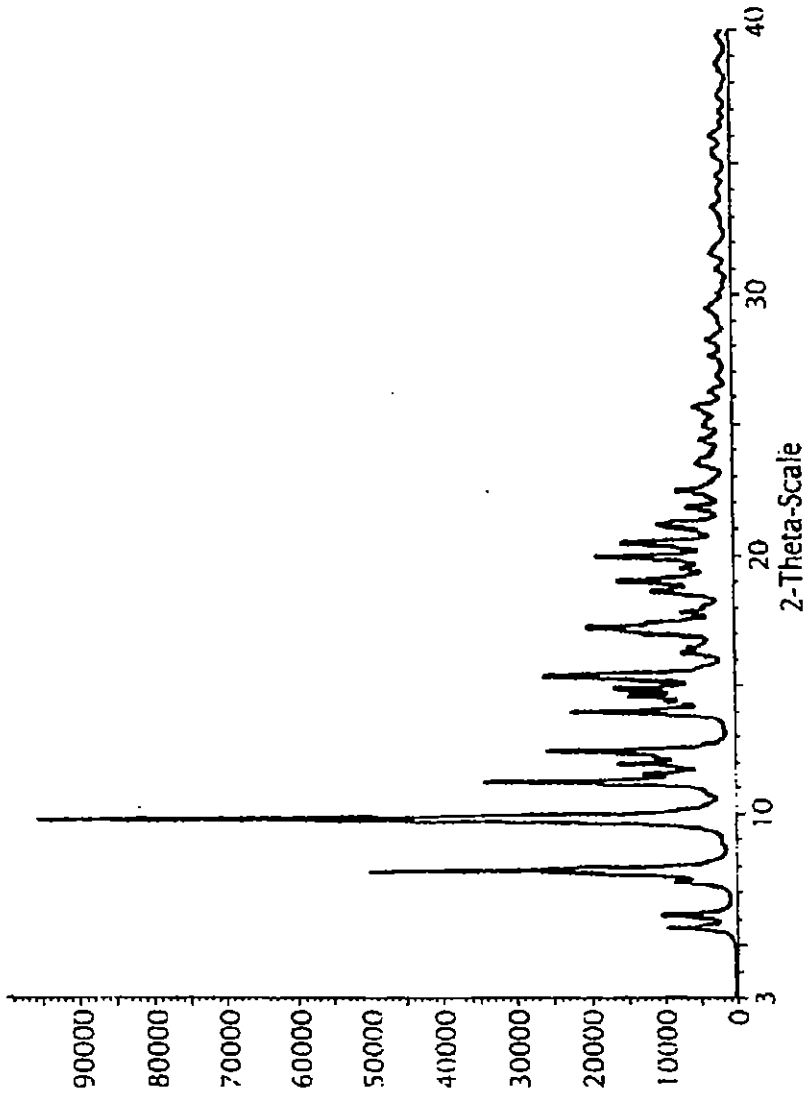
FIG. 12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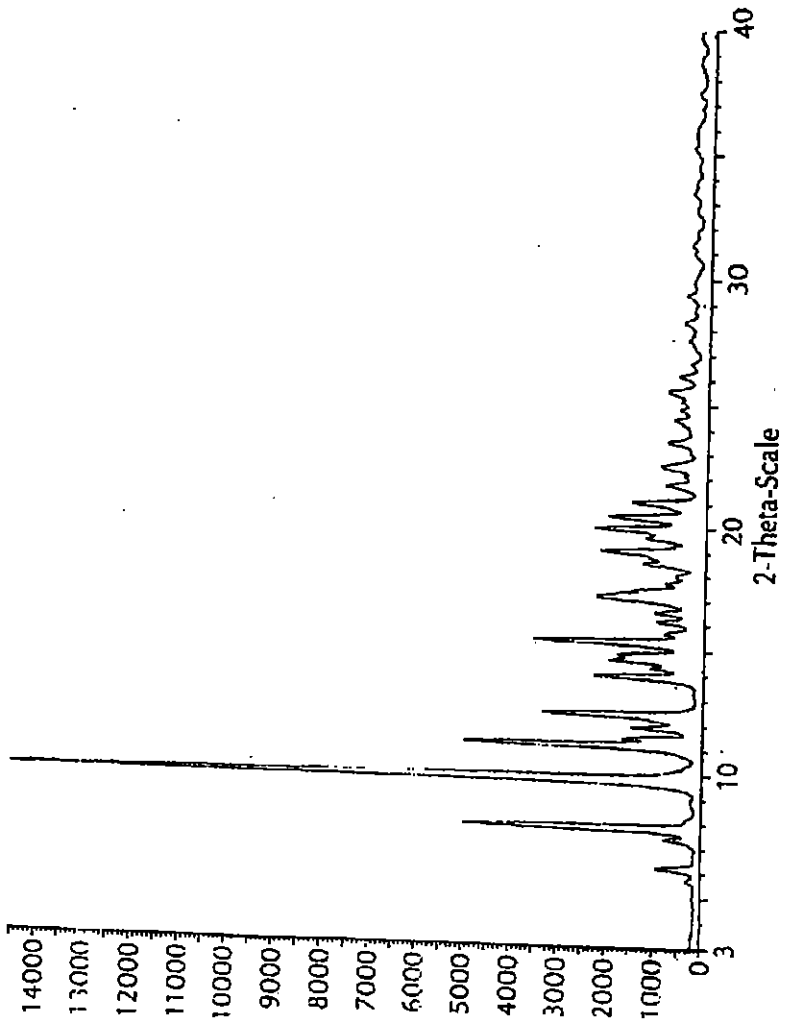
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FIG. 14

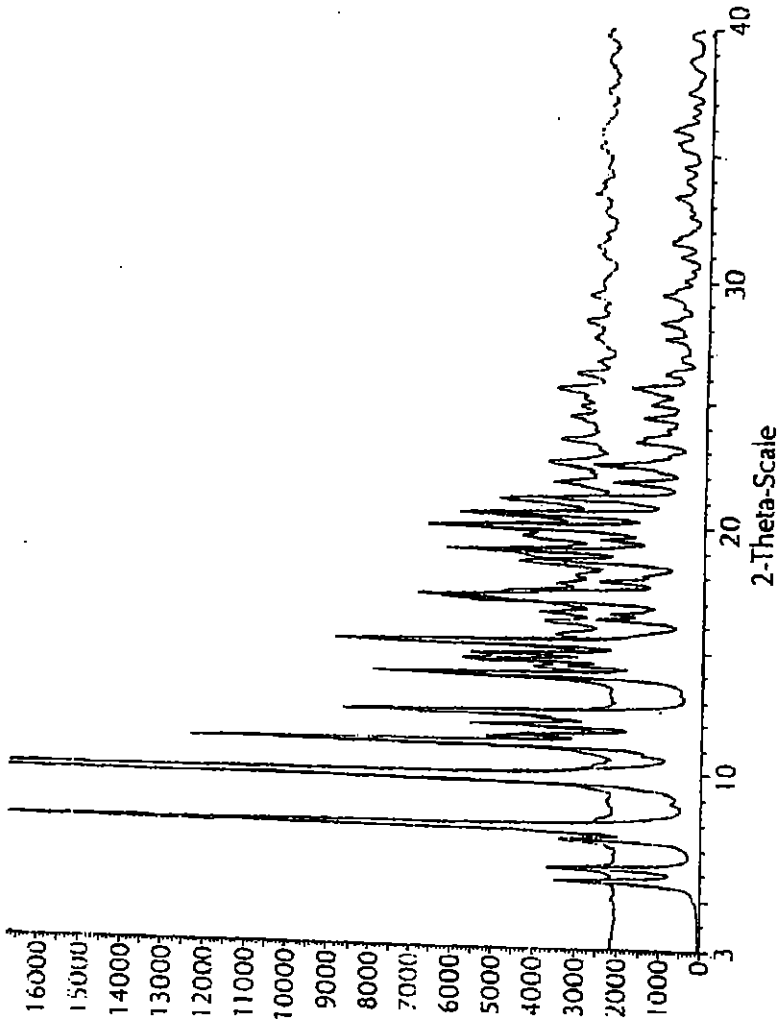
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FIG. 15

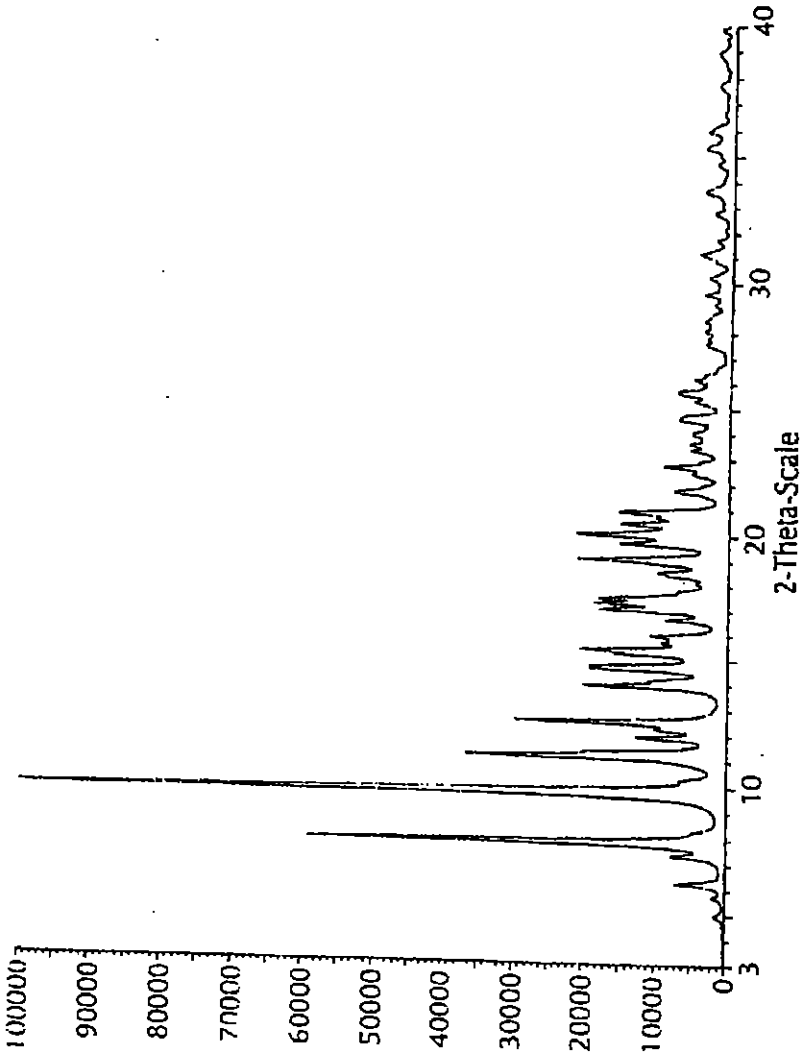
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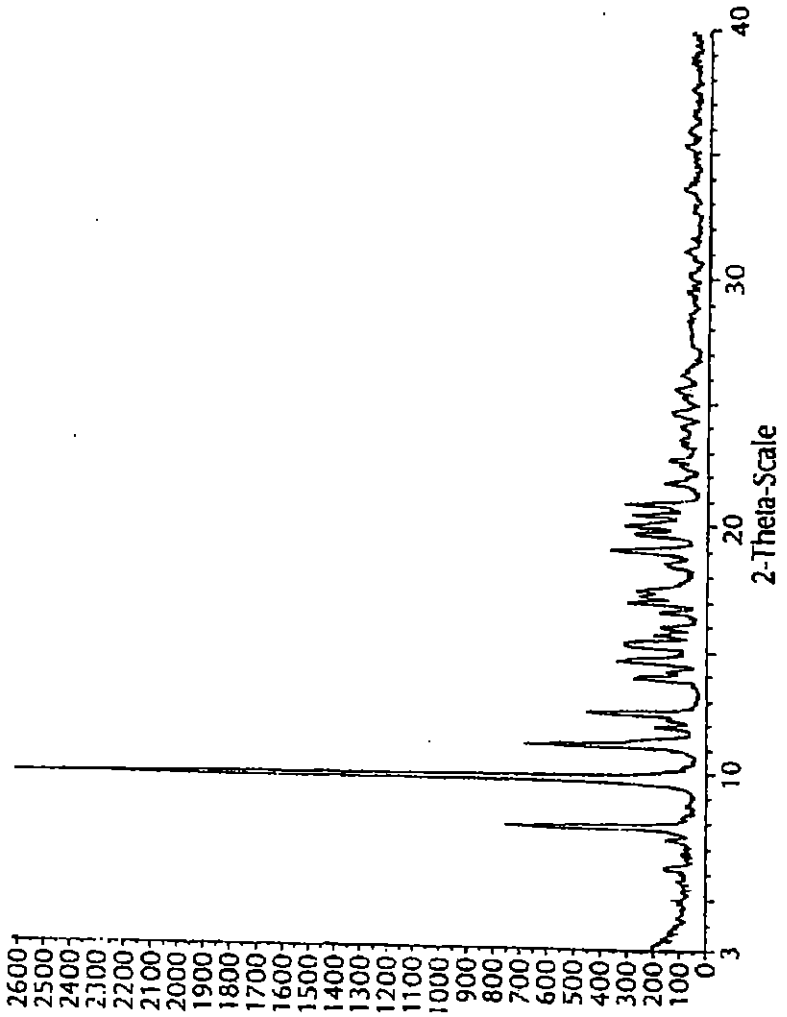
FIG. 16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1600
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1300
1200
1100
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900
800
700
600
500
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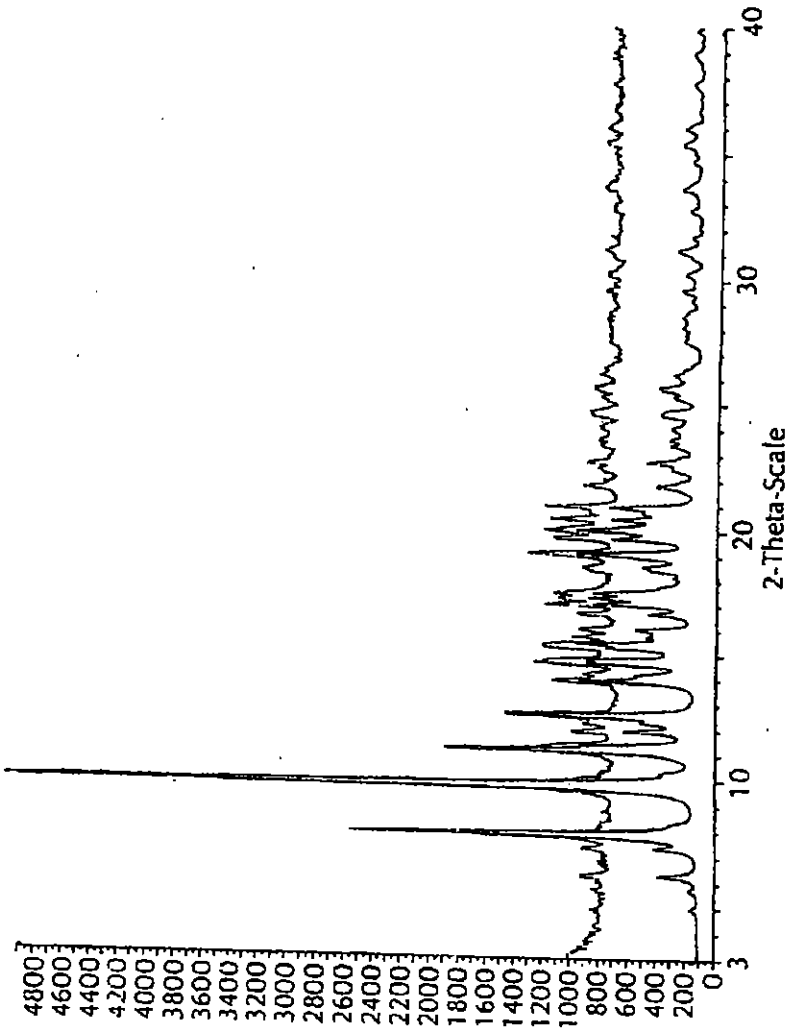
300
200
100
0
3
10
20
30
40
2-Theta-Scale

FIG. 17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4000
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2400
2200
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1800
1600
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1200
1000
800
600
400
200
0
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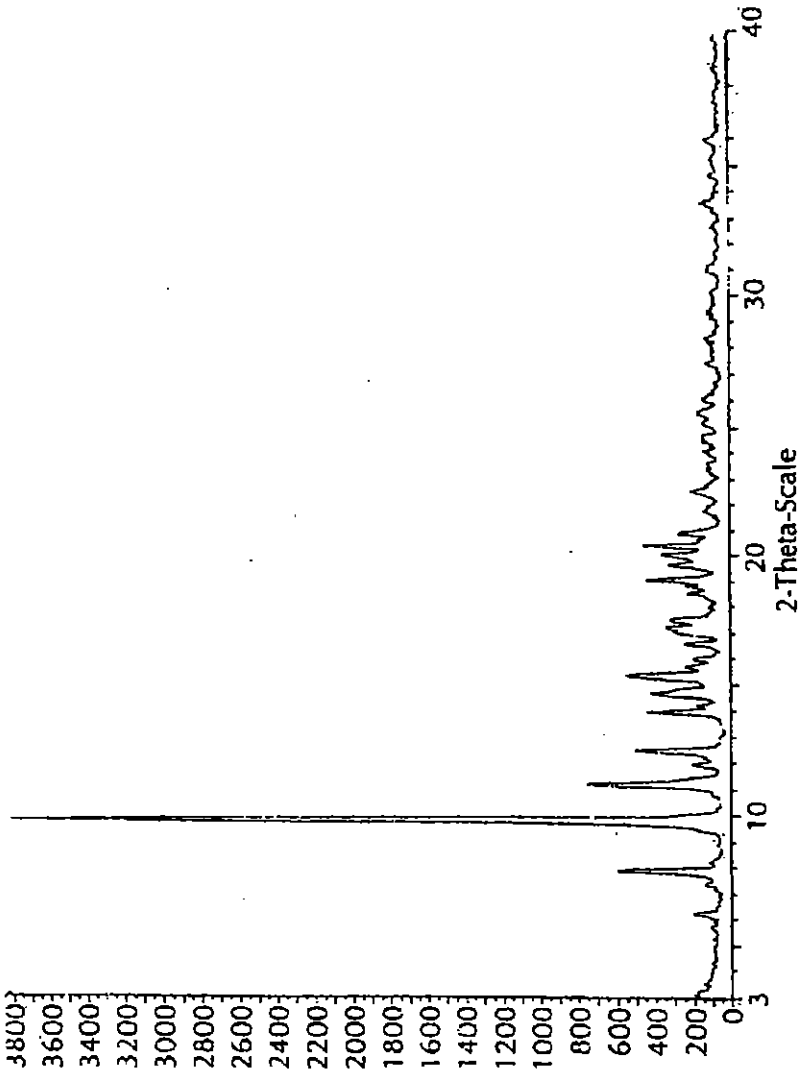
20
30
40
2-Theta-Scale

FIG. 18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2400
2200
2000
1800
1600
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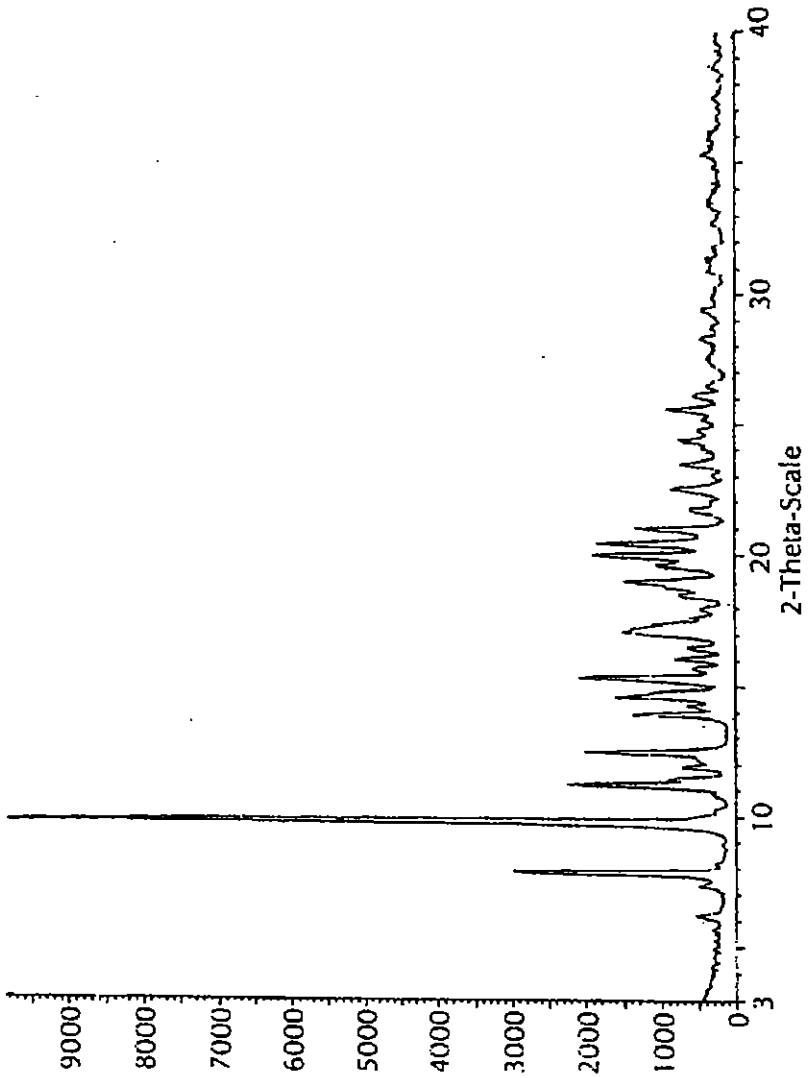
1200
1000
800
600
400
200
0
3
10
20
30
40
2-Theta-Scale

FIG. 19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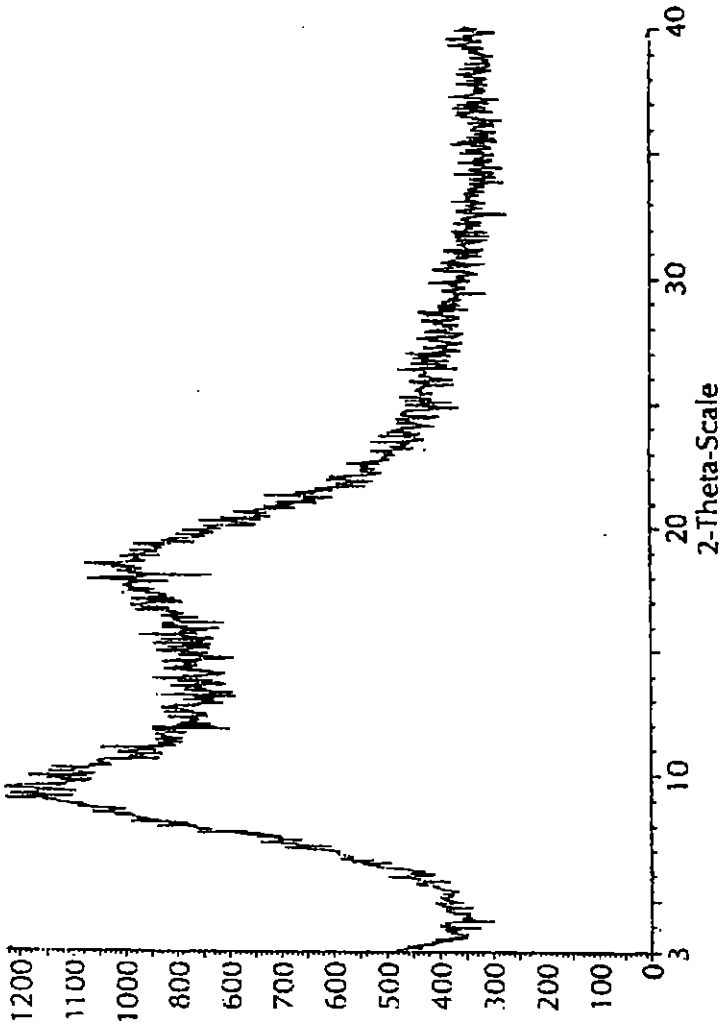
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40
2-Theta-Scale

FIG. 20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600
700
600
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200
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10
20
30
40
2-Theta-Scale

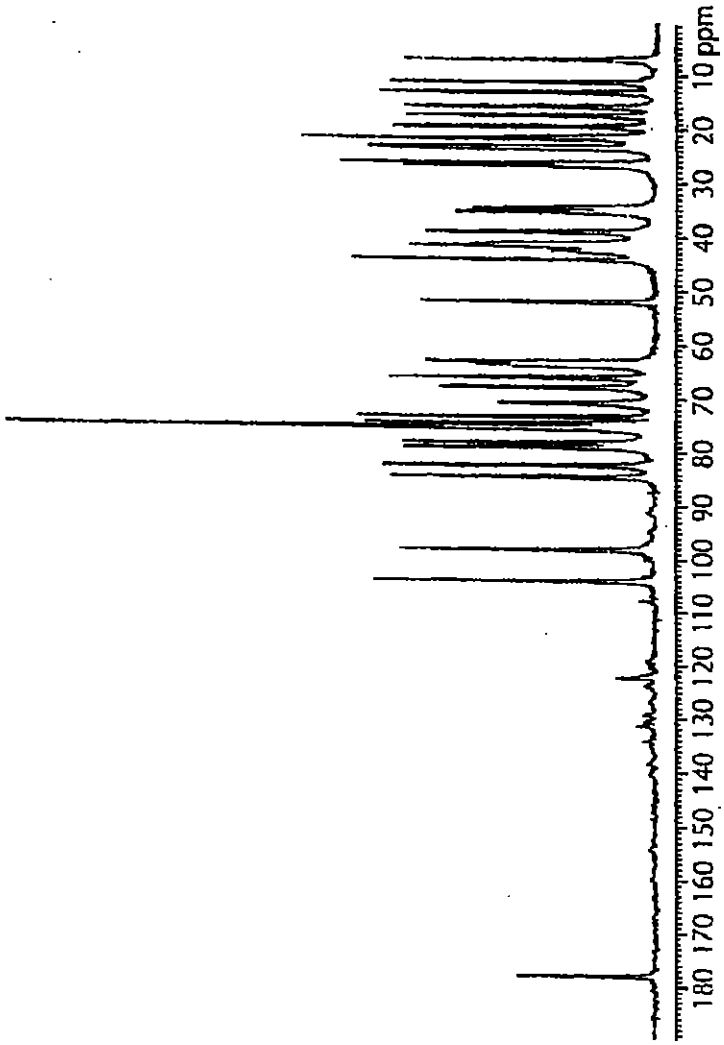


FIG. 21

FIG. 22

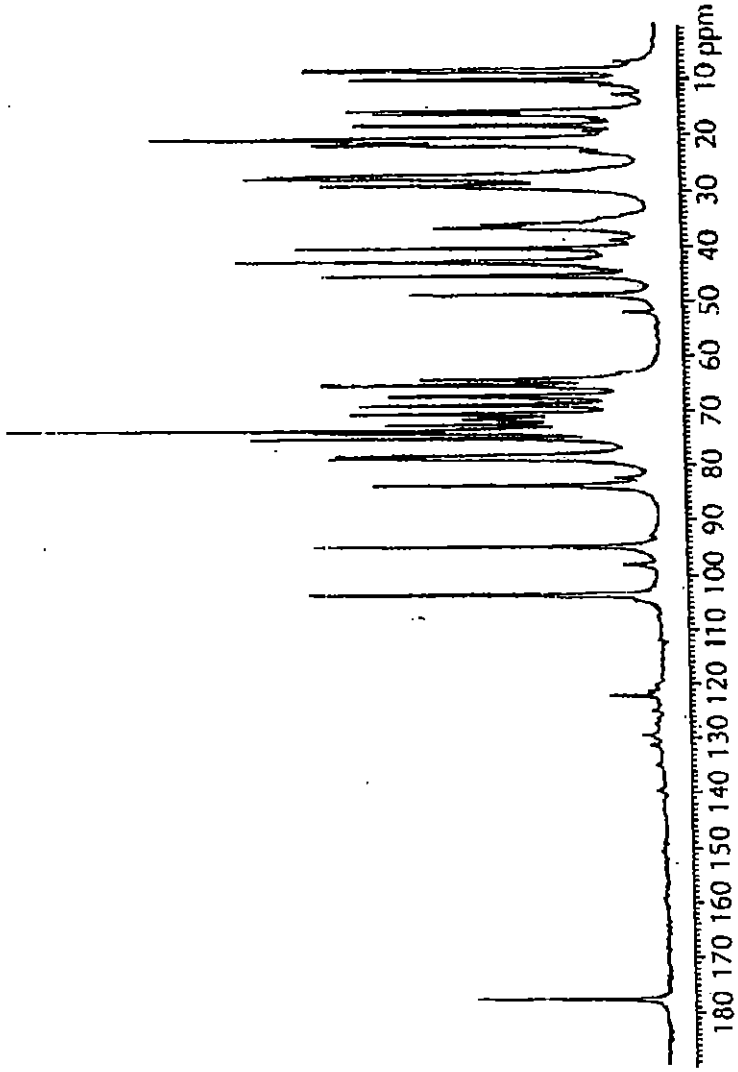


FIG. 23

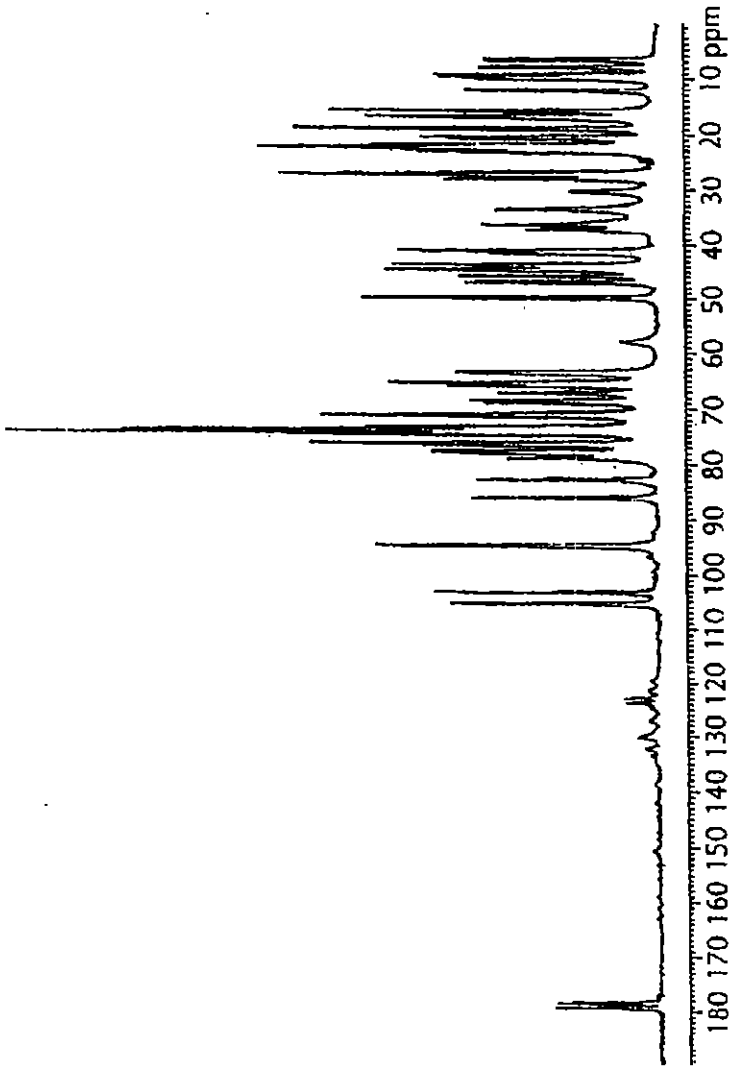
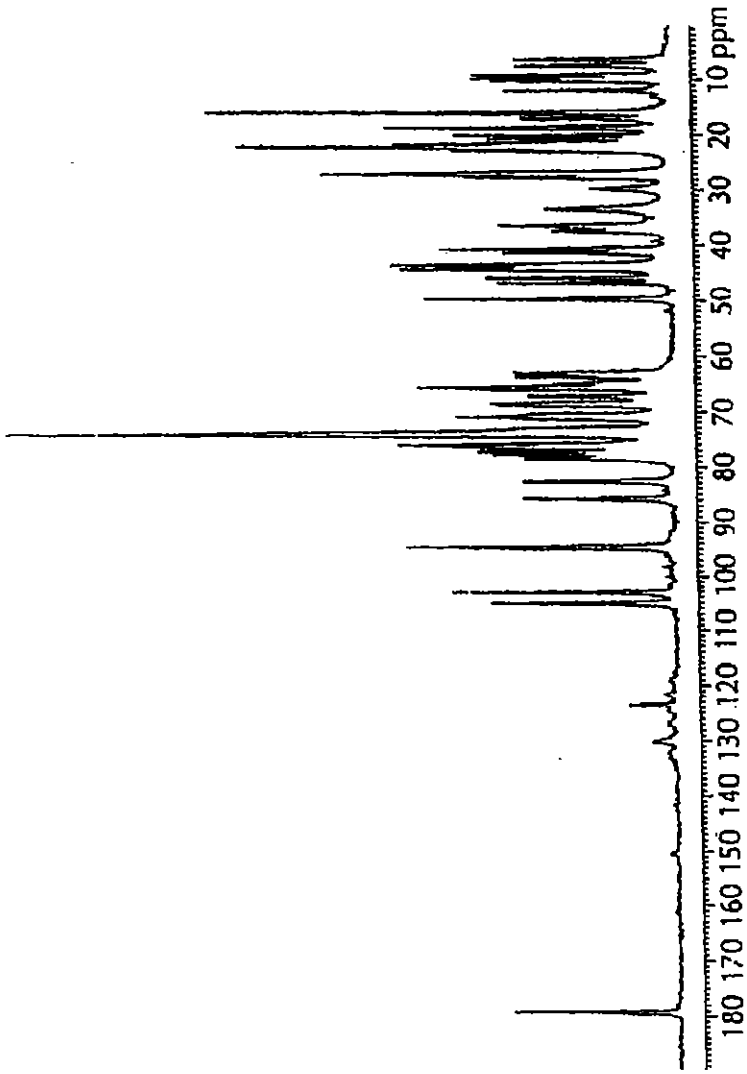


FIG. 24



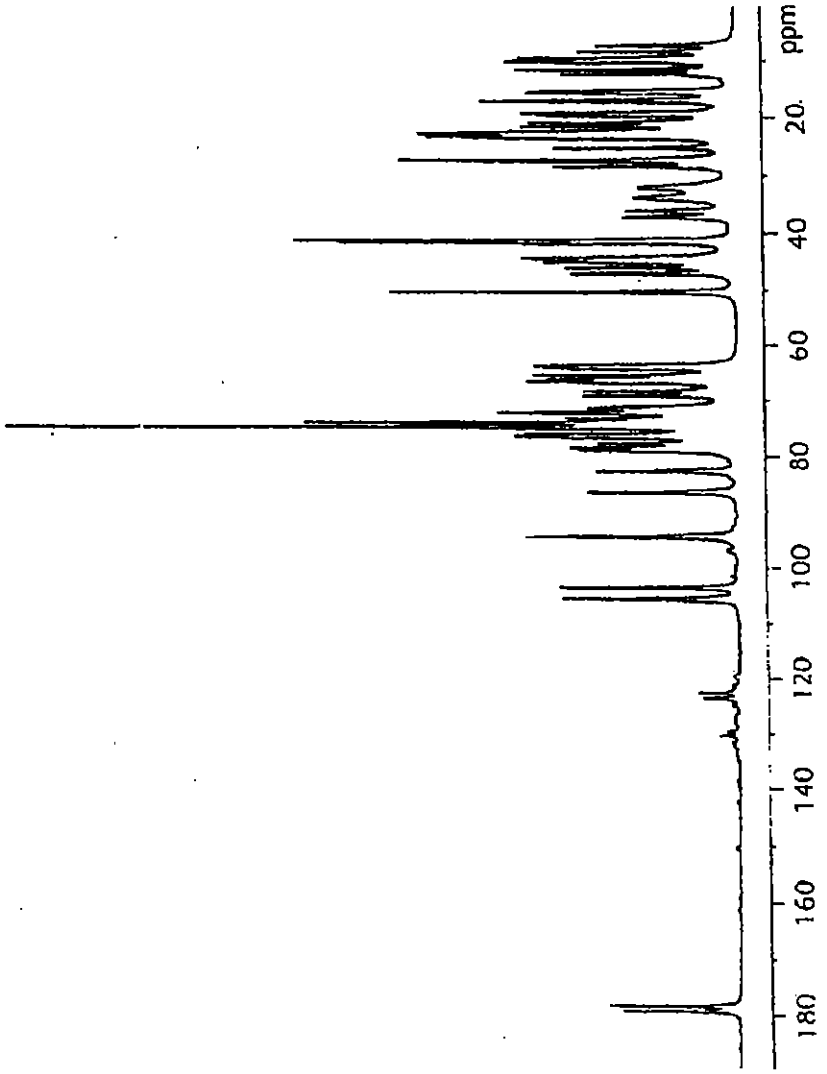


FIG. 25

FIG. 26

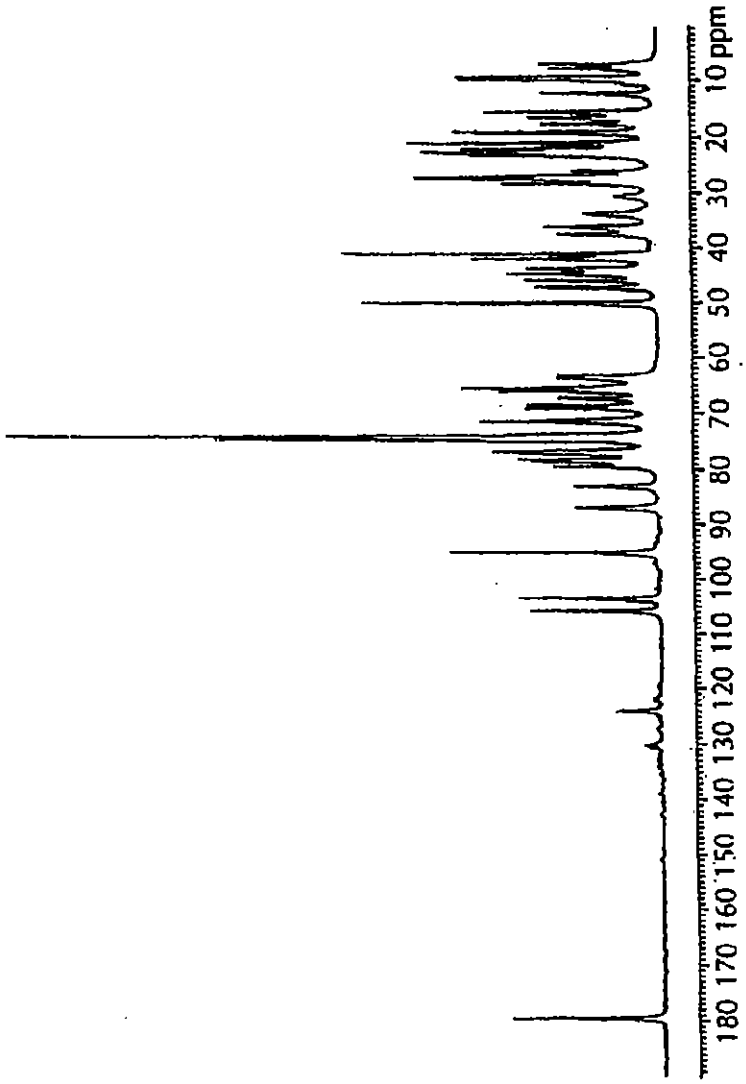
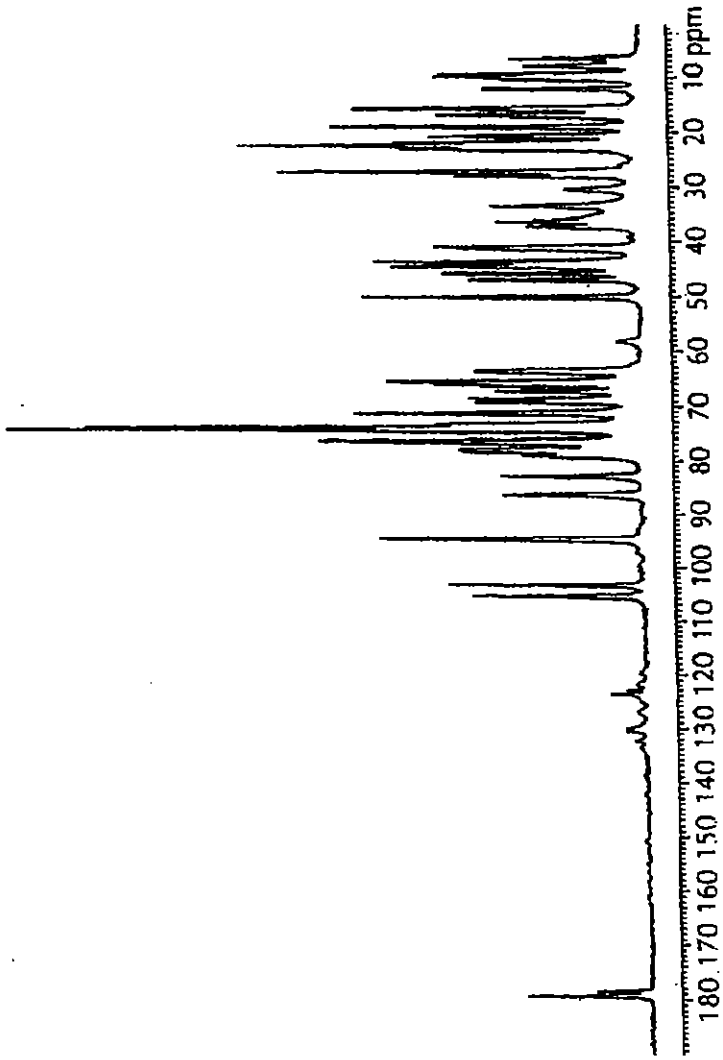


FIG. 27



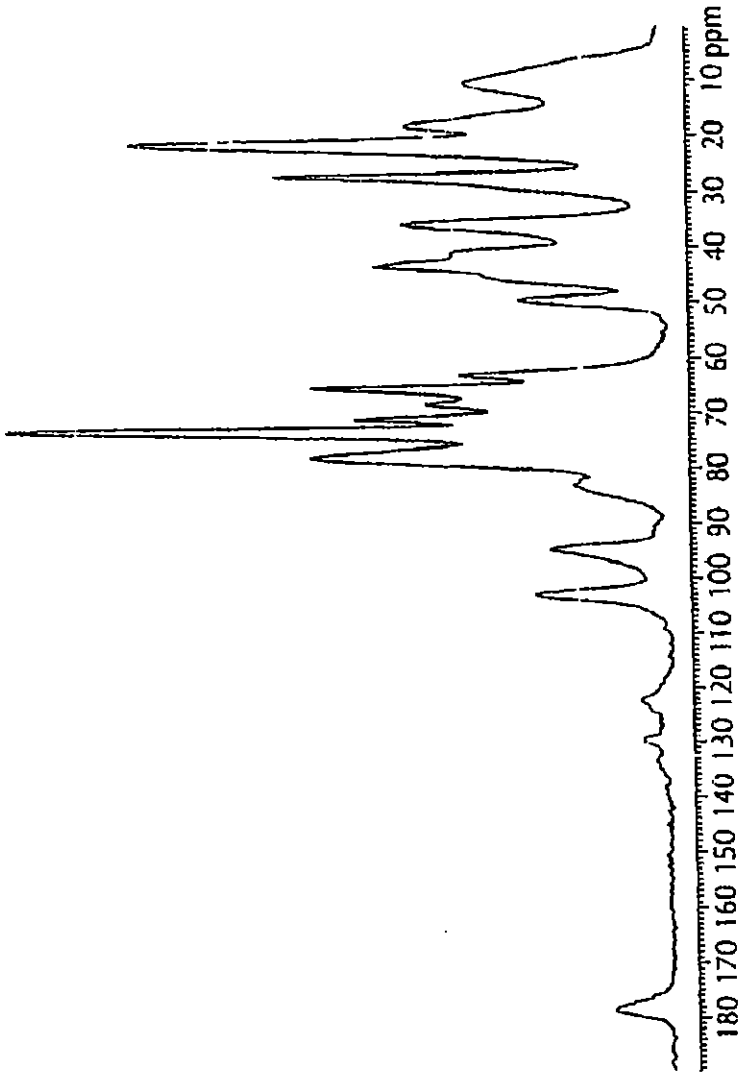


FIG. 28

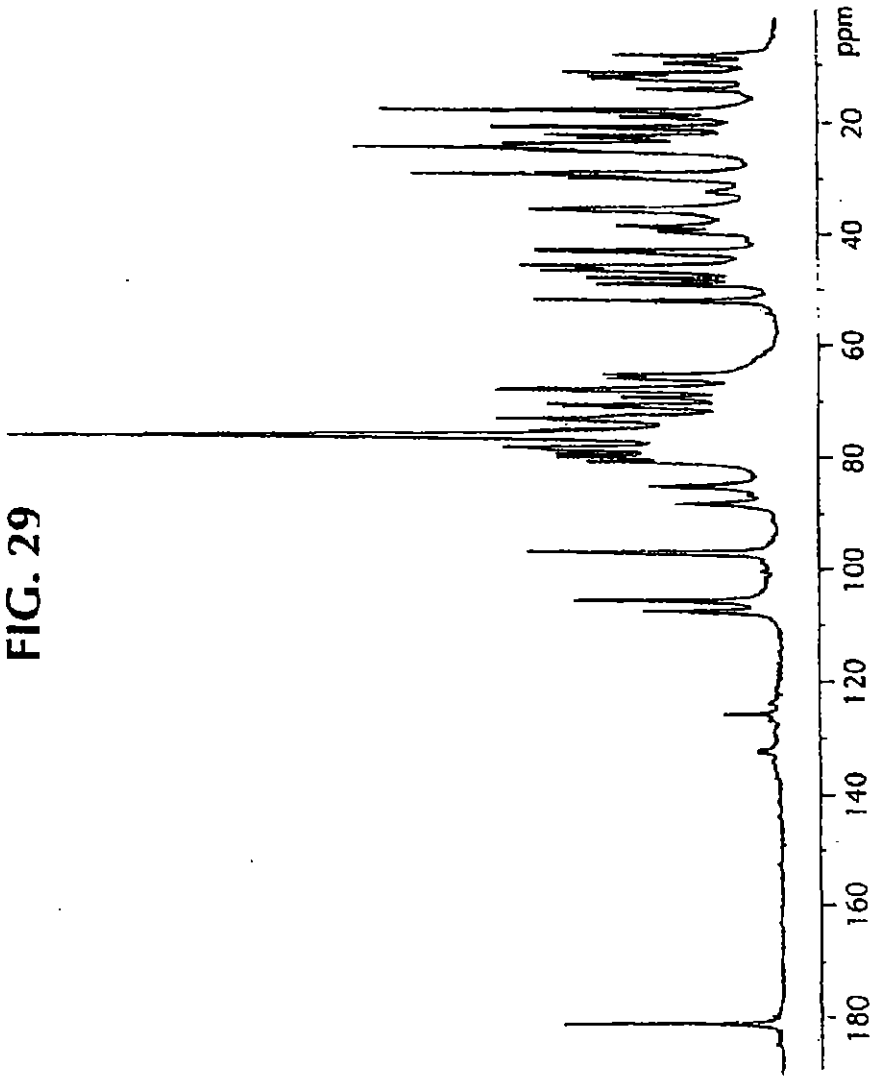


FIG. 29

FIG. 30

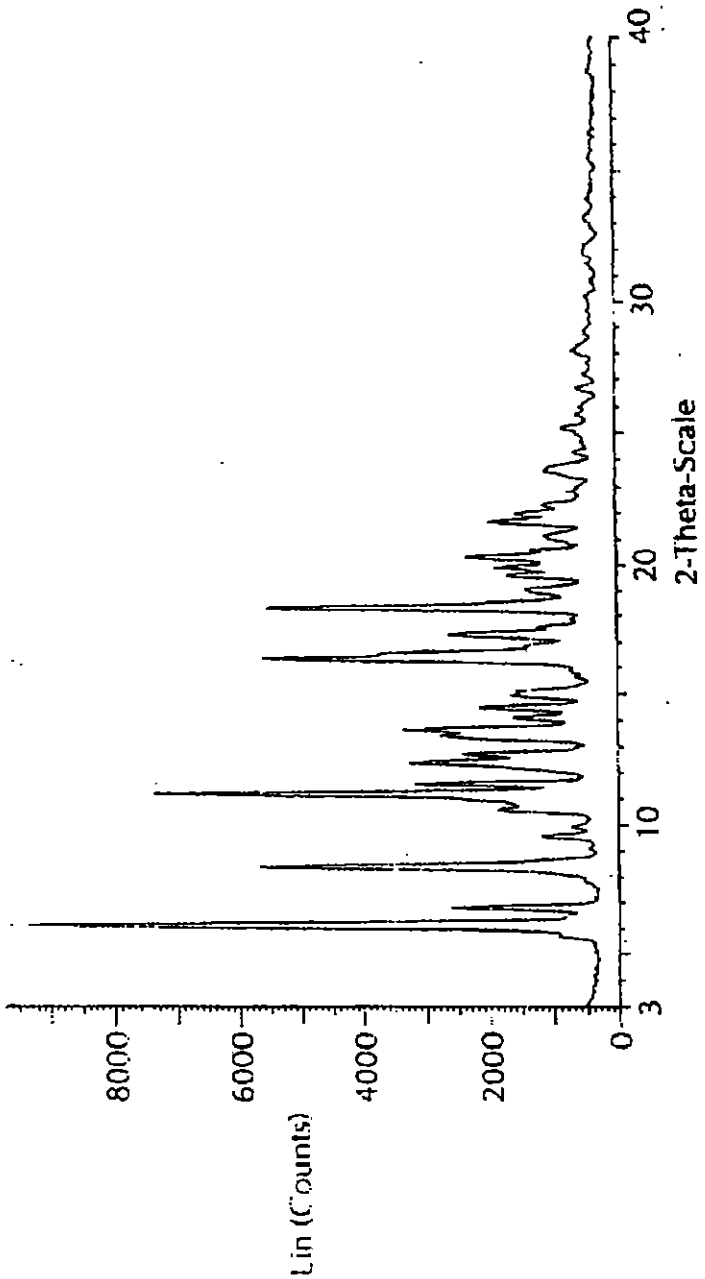


FIG. 31

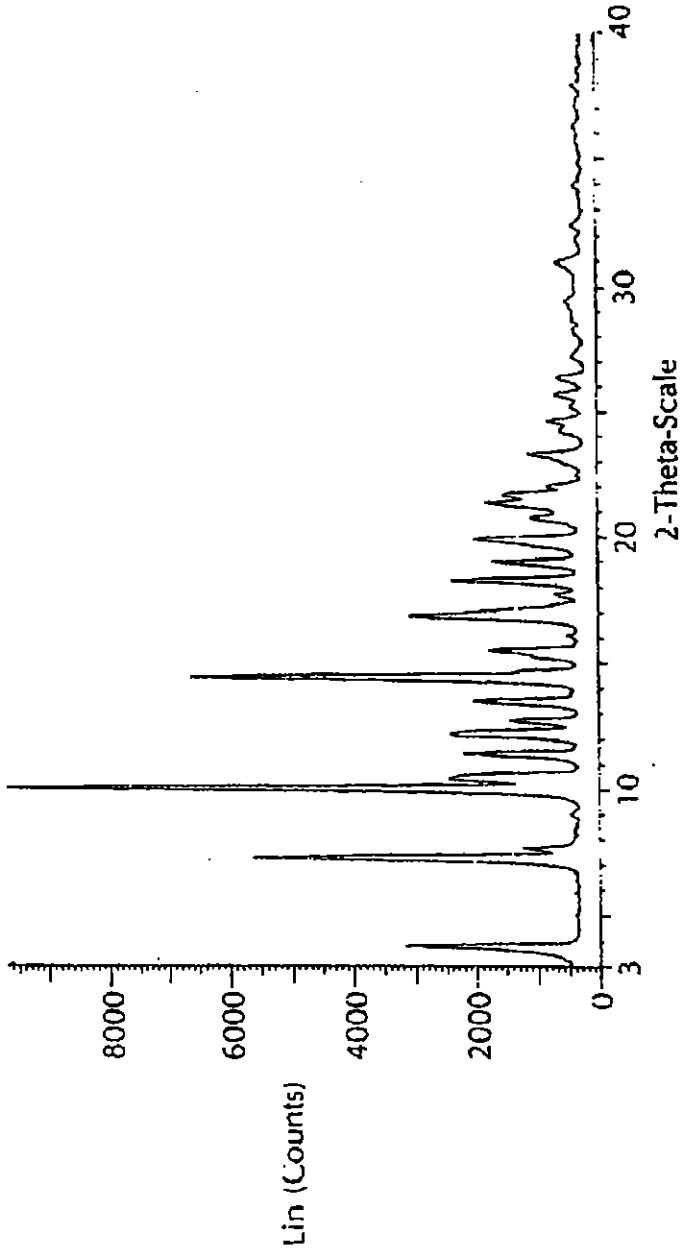


FIG. 32

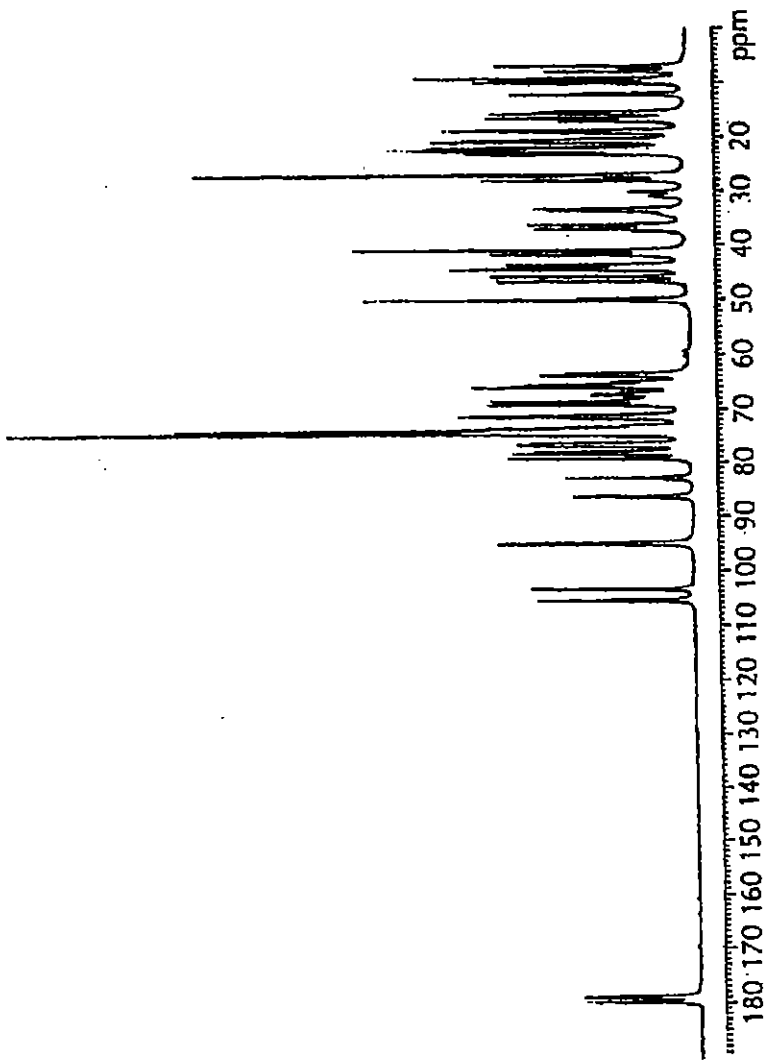
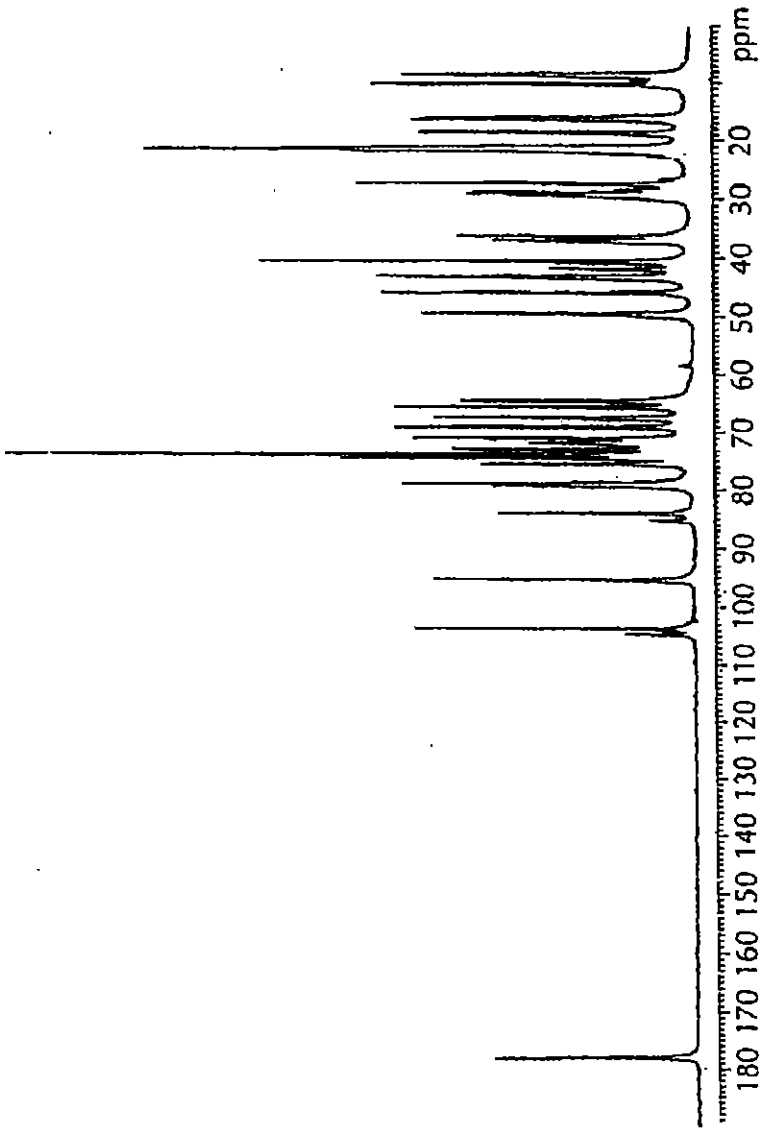


FIG. 33



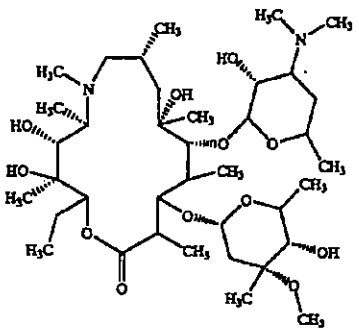
CRYSTAL FORMS OF AZITHROMYCIN

This application claims the benefit of U.S. Provisional Application Ser. No. 60/292,565, filed May 22, 2001; U.S. Provisional Application Ser. No. 60/297,741, filed Jun. 12, 2001; and U.S. Provisional Application Ser. No. 60/343,041, filed Dec. 21, 2001, the contents of the aforementioned provisional patent applications are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

This invention relates to crystal forms of azithromycin. Azithromycin is sold commercially and is an effective antibiotic in the treatment of a broad range of bacterial infections. The crystal forms of this invention are likewise useful as antibiotic agents in mammals, including man, as well as in fish and birds.

Azithromycin has the following structural formula:



Azithromycin is described and claimed in U.S. Pat. Nos. 4,517,359 and 4,474,768. It is also known as 9-deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.

Other patents or patent applications which directly or indirectly cover azithromycin include: EP 298,650 which claims azithromycin dihydrate; U.S. Pat. No. 4,963,531 which claims a method of treating a strain of *Toxoplasma gondii* species; U.S. Pat. No. 5,633,006 which claims a chewable tablet or liquid suspension pharmaceutical composition having reduced bitterness; U.S. Pat. No. 5,686,587 which claims an intermediate useful in the preparation of azithromycin; U.S. Pat. No. 5,605,889 which claims an oral dosage form that reduces the "food effect" associated with the administration of azithromycin; U.S. Pat. No. 6,068,859 which claims a controlled dosage form containing azithromycin; U.S. Pat. No. 5,498,699 which claims a composition containing azithromycin in combination with bivalent or trivalent metals; EP 925,789 which claims a method of treating eye infections; Chinese patent application CN 1123279A which relates to water soluble salts of azithromycin; Chinese patent application CN 1046945C which relates to azithromycin sodium dihydrogenphosphate double salts; Chinese patent application CN 1114960A which relates to azithromycin crystals, Chinese patent application CN 1161971A which relates to azithromycin crystals; Chinese patent application CN 1205338A which relates to a method of preparing water soluble salts of azithromycin; International Publication WO 00/32203 which relates to an ethanolate of azithromycin; and European patent application EP 984,020 which relates to an azithromycin monohydrate isopropanol clathrate.

SUMMARY OF THE INVENTION

The present invention relates to crystal forms of azithromycin. As used herein, the term "crystal form(s)" or "form(s)", unless otherwise noted, means one or more crystal forms of azithromycin.

In particular, the present invention relates to a crystal form of azithromycin wherein said crystal form is selected from forms C, D, E, F, G, H, J, M, N, O, P, Q and R wherein said forms are as defined herein. Forms F, G, H, J, M, N, O, and P belong to family I azithromycin and belong to a monoclinic $P2_1$ space group with cell dimensions of a=16.3±0.3 Å, b=16.2±0.3 Å, c=18.4±0.3 Å and beta=109±2°. Forms C, D, E and R belong to family II azithromycin and belong to an orthorhombic $P2_12_12_1$ space group with cell dimensions of a=8.9±0.4 Å, b=12.3±0.5 Å and c=45.8±0.5 Å. Form Q is distinct from families I and II.

Form F azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.0.5C_2H_5OH$ in the single crystal structure, being azithromycin monohydrate hemi-ethanol solvate. Form F is further characterized as containing 2–5% water and 1–4% ethanol by weight in powder samples and having powder X-ray diffraction 2θ peaks as defined in Table 9. The ^{13}C ssNMR (solid state Nuclear Magnetic Resonance) spectrum of form F has two chemical shift peaks at approximately 179±1 ppm, those being 179.5±0.2 ppm and 178.6±0.2 ppm, a set of five peaks between 6.4 to 11.0 ppm, and ethanol peaks at 58.0±0.5 ppm and 17.2±0.5 ppm. The solvent peaks can be broad and relatively weak in intensity.

The invention also relates to substantially pure form F azithromycin, form F azithromycin substantially free of form G azithromycin and form F azithromycin substantially free of azithromycin dihydrate.

The invention further relates to methods of preparing form F azithromycin by treating azithromycin with ethanol to complete dissolution at 40–70° C. and cooling with reduction of ethanol or addition of water to effect crystallization. Also included are methods of making substantially pure form F azithromycin, form F azithromycin substantially free of form G azithromycin and form F azithromycin substantially free of azithromycin dihydrate.

Form G azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.1.5H_2O$ in the single crystal structure, being azithromycin sesquihydrate. Form G is further characterized as containing 2.5–6% water and <1% organic solvent(s) by weight in powder samples and having powder X-ray diffraction 2θ peaks as defined in Table 9. The ^{13}C ssNMR spectrum of form G has one chemical shift peak at approximately 179±1 ppm, being a peak at 179.5±0.2 ppm (splitting <0.3 ppm may present), and a set of five peaks between 6.3 to 11.0 ppm.

The invention also relates to substantially pure form G azithromycin, and form G azithromycin substantially free of azithromycin dihydrate.

The invention further relates to methods of preparing substantially pure form G azithromycin, and form G azithromycin substantially free of azithromycin dihydrate by treating azithromycin with a mixture of methanol and water or acetone and water to complete dissolution at 40–60° C. and cooling to effect crystallization.

Form H azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.C_3H_8O_2$ being azithromycin monohydrate hemi-1,2 propanediol solvate.

Form J azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.0.5C_3H_7OH$ in the single crystal

structure, being azithromycin monohydrate hemi-n-propanol solvate. Form J is further characterized as containing 2–5% water and 1–5% 1-propanol by weight in powder samples and having powder X-ray diffraction 2θ peaks as defined in Table 9. The ^{13}C ssNMR spectrum of form J has two chemical shift peaks at approximately 179±1 ppm, those being 179.6±0.2 ppm and 178.4±0.2 ppm, a set of five peaks between 6.6 to 11.7 ppm and an n-propanol peak at 25.2±0.4 ppm. The solvent peak can be broad and relatively weak in intensity.

The invention further relates to methods of preparing form J by treating azithromycin with n-propanol to complete dissolution at 25–55° C. and cooling with addition of water to effect crystallization.

Form M azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.0.5C_3H_7OH$, being azithromycin monohydrate hemi-isopropanol solvate. Form M is further characterized as containing 2–5% water and 1–4% 2-propanol by weight in powder samples and having powder X-ray diffraction 2θ peaks as defined in Table 9. The ^{13}C ssNMR spectrum of form M has one chemical shift peak at approximately 179±1 ppm, being 179.6±0.2 ppm, a peak at 41.9±0.2 ppm and a set of six peaks between 6.9 to 16.4 ppm and an isopropanol peak at 26.0±0.4 ppm. The solvent peak can be broad and relatively weak in intensity.

The invention also relates to substantially pure form M azithromycin, form M azithromycin substantially free of form G azithromycin and form M azithromycin substantially free of azithromycin dihydrate.

The invention further relates to methods of preparing substantially pure form M azithromycin, form M azithromycin substantially free of form G azithromycin and form M azithromycin substantially free of azithromycin dihydrate by treating azithromycin with isopropanol to complete dissolution at 40–60° C. and reduction of isopropanol followed by cooling or cooling followed by addition of water to effect crystallization.

Form N azithromycin is a mixture of isomorphs of Family I. The mixture may contain variable percentages of isomorphs, F, G, H, J, M and others, and variable amounts of water and organic solvents, such as ethanol, isopropanol, n-propanol, propylene glycol, acetone, acetonitrile, butanol, pentanol, etc. The weight percent of water can range from 1–5% and the total weight percent of organic solvents can be 2–5% with each solvent content of 0.5 to 4%. The samples of form N display all characteristic peaks of members of Family I in various proportions. Form N may be characterized as 'mixed crystals' or "crystalline solid solutions' of Family I isomorphs.

Form N displays chemical shifts as a combination of isomorphs in Family I. The peaks may vary in chemical shift ppm within ±0.2 ppm and in relative intensities and width due to the mixing of variable proportion of isomorphs contained in the form N crystalline solid solution.

Form P azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.0.5C_5H_{12}O$ being azithromycin monohydrate hemi-n-pentanol solvate.

Form Q azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.0.5C_4H_8O$ being azithromycin monohydrate hemi-tetrahydrofuran solvate.

Form R azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.C_5H_{12}O$ being azithromycin monohydrate mono-methyl tert-butyl ether solvate.

Form D azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.C_6H_{12}$ in its single crystal structure, being azithromycin monohydrate monocyclohexane solvate. Form D is further characterized as containing 2–6% water and 3–12% cyclohexane by weight in powder samples and having representative powder X-ray diffraction 2θ peaks as defined in Table 9. The ^{13}C ssNMR spectrum of form D displays has one chemical shift peak at approximately 179±1 ppm, being 178.1±0.2 ppm and peaks at 103.9±0.2ppm, 95.1±0.2 ppm, 84.2±0.2 ppm, and a set of 3 peaks between 8.4 to 11 ppm.

The invention further relates to methods of preparing form D by slurrying azithromycin dihydrate with cyclohexane.

Form E azithromycin is of the formula $C_{38}H_{72}N_2O_{12}.H_2O.C_4H_8O$ being azithromycin monohydrate mono-tetrahydrofuran solvate.

The invention further relates to azithromycin in an amorphous state and a method of preparing amorphous azithromycin that comprises the removal of water and/or solvents from the azithromycin crystal lattice. The X-ray diffraction powder pattern for amorphous azithromycin displays no sharp 2θ peaks but has two broad rounded peaks. The first peak occurs between 4° and 13°. The second peak occurs between 13° and 25°.

The invention also relates to pharmaceutical compositions for the treatment of a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises a therapeutically effective amount of the crystalline compounds referred to above, or amorphous azithromycin, and a pharmaceutically acceptable carrier.

The invention also relates to a method of treating a bacterial infection or a protozoa infection in a mammal, fish, or bird which comprises administering to said mammal, fish or bird a therapeutically effective amount of the crystalline compounds referred to above, or amorphous azithromycin.

The present invention also relates to methods of preparing crystal forms of azithromycin which comprise the slurrying of azithromycin in an appropriate solvent or the dissolution of azithromycin in a heated organic solvent or organic solvent/water solution and precipitating the crystalline azithromycin by cooling the solution with reduction of solvent volume or by dissolving azithromycin in a solvent or solvent mixture and precipitating crystalline azithromycin by the addition of water to the solution. Azithromycin in amorphous state is prepared by heating crystalline azithromycin in a vacuum.

The term "treatment", as used herein, unless otherwise indicated, means the treatment or prevention of a bacterial infection or protozoa infection as provided in the method of the present invention, including curing, reducing the symptoms of or slowing the progress of said infection. The terms "treat" and "treating" are defined in accord the foregoing term "treatment".

The term "substantially free" when referring to a designated crystalline form of azithromycin means that there is less than 20% (by weight) of the designated crystalline form(s) present, more preferably, there is less than 10% (by weight) of the designated form(s) present, more preferably, there is less than 5% (by weight) of the designated form(s) present, and most preferably, there is less than 1% (by weight) of the designated crystalline form(s) present. For instance, form F azithromycin substantially free of azithromycin dihydrate means form F with 20% (by weight) or less of azithromycin dihydrate, more preferably, 10% (by weight) or less of azithromycin dihydrate, most preferably, 1% (by weight) of azithromycin dihydrate.

The term "substantially pure" when referring to a designated crystalline form of azithromycin means that the des-

ignated crystalline form contains less than 20% (by weight) of residual components such as alternate polymorphic or isomorphic crystalline form(s) of azithromycin. It is preferred that a substantially pure form of azithromycin contain less than 10% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin, more preferred is less than 5% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin, and most preferably less than 1% (by weight) of alternate polymorphic or isomorphic crystalline forms of azithromycin.

The term "substantially in the absence of azithromycin dihydrate" when referring to bulk crystalline azithromycin or a composition containing crystalline azithromycin means the crystalline azithromycin contains less than about 5% (by weight) azithromycin dihydrate, more preferably less than about 3% (by weight) azithromycin dihydrate, and most preferably less than 1% (by weight) azithromycin dihydrate.

As used herein, unless otherwise indicated, the term "bacterial infection(s)" or "protozoa infection" includes bacterial infections and protozoa infections and diseases caused by such infections that occur in mammals, fish and birds as well as disorders related to bacterial infections and protozoa infections that may be treated or prevented by administering antibiotics such as the compound of the present invention. Such bacterial infections and protozoa infections and disorders related to such infections include, but are not limited to, the following: pneumonia, otitis media, sinusitus, bronchitis, tonsillitis, and mastoiditis related to infection by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Staphylococcus aureus*, or *Peptostreptococcus* spp.; pharynigitis, rheumatic fever, and glomerulonephritis related to infection by *Streptococcus pyogenes*, Groups C and G streptococci, *Clostridium diptheriae*, or *Actinobacillus haemolyticum*; respiratory tract infections related to infection by *Mycoplasma pneumoniae, Legionella pneumophila, Streptococcus pneumoniae, Haemophilus influenzae*, or *Chlamydia pneumoniae*; uncomplicated skin and soft tissue infections, abscesses and osteomyelitis, and puerperal fever related to infection by *Staphylococcus aureus*, coagulase-positive staphylococci (i.e., *S. epidermidis, S. hemolyticus*, etc.), *Streptococcus pyogenes, Streptococcus agalactiae*, Streptococcal groups C-F (minute-colony streptococci), viridans streptococci, *Corynebacterium minutissimum, Clostridium* spp., or *Bartonella henselae*; uncomplicated acute urinary tract infections related to infection by *Staphylococcus saprophyticus* or *Enterococcus* spp.; urethritis and cervicitis; and sexually transmitted diseases related to infection by *Chlamydia trachomatis, Haemophilus ducreyi, Treponema pallidum, Ureaplasma urealyticum*, or *Neisserria gonorrheae*; toxin diseases related to infection by *S. aureus* (food poisoning and Toxic shock syndrome), or Groups A, B, and C streptococci; ulcers related to infection by *Helicobacter pylori*; systemic febrile syndromes related to infection by *Borrelia recurrentis*; Lyme disease related to infection by *Borrelia burgdorferi*; conjunctivitis, keratitis, and *dacrocystitis* related to infection by *Chlamydia trachomatis, Neisseria gonorrhoeae, S. aureus, S. pneumoniae, S. pyogenes, H. influenzae*, or *Listeria* spp.; disseminated *Mycobacterium avium* complex (MAC) disease related to infection by *Mycobacterium avium*, or *Mycobacterium intracellulare*; gastroenteritis related to infection by *Campylobacter jejuni*; intestinal protozoa related to infection by *Cryptosporidium* spp.; odontogenic infection related to infection by viridans streptococci; persistent cough related to infection by *Bordetella pertussis*; gas gangrene related to infection by *Clostridium perfringens* or *Bacteroides* spp.; and atherosclerosis related to infection by *Helicobacter pylori* or *Chlamydia pneumoniae*. Also included are atherosclerosis and malaria. Bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in animals include, but are not limited to, the following: bovine respiratory disease related to infection by *P. haem., P. multocida, Mycoplasma bovis*, or *Bordetella* spp.; cow enteric disease related to infection by *E. coli* or protozoa (i.e., coccidia, cryptosporidia, etc.); dairy cow mastitis related to infection by *Staph. aureus, Strep. uberis, Strep. agalactiae, Strep. dysgalactiae, Klebsiella* spp., *Corynebacterium*, or *Enterococcus* spp.; swine respiratory disease related to infection by *A. pleuro., P. multocida*, or *Mycoplasma* spp.; swine enteric disease related to infection by *E. coli, Lawsonia intracellularis, Salmonella*, or *Serpulina hyodysinteriae*; cow footrot related to infection by *Fusobacterium* spp.; cow metritis related to infection by *E. coli*; cow hairy warts related to infection by *Fusobacterium necrophorum* or *Bacteroides nodosus*; cow pink-eye related to infection by *Moraxella bovis*; cow premature abortion related to infection by protozoa (i.e. neosporium); urinary tract infection in dogs and cats related to infection by *E. coli*, skin and soft tissue infections in dogs and cats related to infection by *Staph. epidermidis, Staph. intermedius, coagulase neg. Staph.* or *P. multocida*; and dental or mouth infections in dogs and cats related to infection by *Alcaligenes* spp., *Bacteroides* spp., *Clostridium* spp., *Enterobacter* spp., *Eubacterium, Peptostreptococcus, Porphyromonas*, or *Prevotella*. Other bacterial infections and protozoa infections and disorders related to such infections that may be treated or prevented in accord with the method of the present invention are referred to in J. P. Sanford et al., "The Sanford Guide To Antimicrobial Therapy," 26th Edition, (Antimicrobial Therapy, Inc., 1996).

The present invention also includes isotopically-labeled compounds wherein one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, sulfur, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, and ^{17}O. Such radiolabelled and stable-isotopically labelled compounds are useful as research or diagnostic tools.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a calculated powder X-ray diffraction pattern of azithromycin form A. The scale of the abscissa is degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 2 is an experimental powder X-ray diffraction pattern of azithromycin form A. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 3 is an overlay of FIGS. 1 and 2 with the calculated diffraction patterns of azithromycin form A (FIG. 1) on the bottom and the experimental diffraction pattern of azithromycin form A (FIG. 2) on the top. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 4 is a calculated powder X-ray diffraction pattern of azithromycin form C. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 5 is a calculated powder X-ray diffraction pattern of azithromycin form D. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 6 is an experimental powder X-ray diffraction pattern of azithromycin form D. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 7 is an overlay of FIGS. 5 and 6 with the calculated diffraction pattern of azithromycin form D (FIG. 5) on the bottom and the experimental diffraction pattern of azithromycin form D (FIG. 6) on the top. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 8 is a calculated powder X-ray diffraction pattern of azithromycin form E. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 9 is a calculated powder X-ray diffraction pattern of azithromycin form F. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 10 is an experimental powder X-ray diffraction pattern of azithromycin form F. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 11 is an overlay of FIGS. 9 and 10 with the calculated diffraction pattern of azithromycin form F (FIG. 9) on the bottom and the experimental diffraction pattern of azithromycin form F (FIG. 10) on the top. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 12 is a calculated powder X-ray diffraction pattern of azithromycin form G. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity is counts.

FIG. 13 is an experimental powder X-ray diffraction pattern of azithromycin form G. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 14 is an overlay of FIGS. 12 and 13 with the calculated diffraction pattern of azithromycin form G (FIG. 12) on the bottom and the experimental diffraction pattern of azithromycin form G (FIG. 13) on the top. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 15 is a calculated powder X-ray diffraction pattern of azithromycin form J. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 16 is an experimental powder X-ray diffraction pattern of azithromycin form J. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 17 is an overlay of FIGS. 15 and 16 with the calculated diffraction pattern of azithromycin form J (FIG. 15) on the bottom and the experimental diffraction pattern of azithromycin form J (FIG. 16) on the top. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 18 is an experimental powder X-ray diffraction pattern of azithromycin form M. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 19 is an experimental powder X-ray diffraction pattern of azithromycin form N. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 20 is an experimental powder X-ray diffraction pattern of amorphous azithromycin. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 21 is a ^{13}C solid state NMR spectrum of azithromycin form A.

FIG. 22 is a ^{13}C solid state NMR spectrum of azithromycin form D.

FIG. 23 is a ^{13}C solid state NMR spectrum of azithromycin form F.

FIG. 24 is a ^{13}C solid state NMR spectrum of azithromycin form G.

FIG. 25 is a ^{13}C solid state NMR spectrum of azithromycin form J.

FIG. 26 is a ^{13}C solid state NMR spectrum of azithromycin form M.

FIG. 27 is a ^{13}C solid state NMR spectrum of azithromycin form N.

FIG. 28 is a ^{13}C solid state NMR spectrum of amorphous azithromycin.

FIG. 29 is a ^{13}C solid state NMR spectrum of a pharmaceutical tablet containing form G azithromycin.

FIG. 30 is an experimental powder X-ray diffraction pattern of azithromycin form Q. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 31 is an experimental powder X-ray diffraction pattern of azithromycin form R. The scale of the abscissa is in degrees 2-theta (2 θ). The ordinate is the intensity in counts.

FIG. 32 is a ^{13}C solid state NMR spectrum of azithromycin form H.

FIG. 33 is a ^{13}C solid state NMR spectrum of azithromycin form R.

DETAILED DESCRIPTION OF THE INVENTION

Azithromycin has been found to exist in different crystalline forms. A dihydrate, form A, and a non-stroichiometric hydrate, form B, are disclosed in European Patent EP 298 650 and U.S. Pat. No. 4,512,359, respectively. Sixteen other forms have been discovered, namely forms C, D, E, F, G, H, I, J, K, L, M, N, O, P, Q and R. These forms are either hydrates or hydrate/solvates of azithromycin free base. Forms L and K are the metastable lower hydrate forms of A, detected at high temperature. Crystal structures of forms A, C, D, E, F, G, H, J and O have been solved. The structural data of these crystal forms are given below:

TABLE 1

Crystallographic data of azithromycin form A.

	Form A
Empirical formula	$C_{38}H_{72}N_2O_{12}\cdot 2H_2O$
Formula weight	785.2
Crystal size (mm)	0.19 × 0.24 × 0.36
Space group	$P2_12_12_1$, orthorhombic
Unit cell dimensions	a = 14.735 (5) Å
	b = 16.844 (7) Å
	c = 17.81 (1) Å
	α = 90°
	β = 90°
	γ = 90°
Z (per formula)	4
Density (g/cm^3)	1.18
R	0.060

TABLE 2

Crystallographic data of azithromycin form C.

	Form C
Empirical formula	$C_{38}H_{72}N_2O_{12}.H_2O$
Formula weight	767.15
Crystal size (mm)	0.16 x 0.16 x 0.19
Space group	$P2_12_12_1$ orthorhombic
Unit cell dimensions	a = 8.809 (3) Å b = 12.4750 (8) Å c = 45.59 (3) Å α = 90° β = 90° γ = 90°
Z (per formula)	4
Density (g/cm³)	1.01
R	0.106

TABLE 3

Crystallographic data of azithromycin form D.

	Form D
Empirical formula	$C_{38}H_{72}N_2O_{12}.H_2O.C_6H_{12}$
Formula weight	851.15
Crystal size (mm)	0.52 x 0.32 x 0.16
Space group	$P2_12_12_1$ orthorhombic
Unit cell dimensions	a = 8.8710 (10) Å b = 12.506 (2) Å c = 45.697 (7) Å α = 90° β = 90° γ = 90°
Z (per formula)	4
Density (g/cm³)	1.12
R	0.0663

TABLE 4

Crystallographic data of azithromycin form E.

	Form E
Empirical formula	$C_{38}H_{72}N_2O_{12}.H_2O.C_6H_6O$
Formula weight	839.2
Crystal size (mm)	0.17 x 0.19 x 0.20
Space group	$P2_12_12_1$ orthorhombic
Unit cell dimensions	a = 8.869 (3) Å b = 12.086 (3) Å c = 46.00 (1) Å α = 90° β = 90° γ = 90°
Z (per formula)	4
Density (g/cm³)	1.13
R	0.087

TABLE 5

Crystallographic data of azithromycin form F.

	Form F
Empirical formula	$C_{38}H_{72}N_2O_{12}.H_2O.0.5C_6H_6O$
Crystal size (mm)	0.14 x 0.20 x 0.24
Formula weight	790.2
Space group	$P2_1$ monoclinic
Unit cell dimensions	a = 16.281 (2) Å b = 16.293(1) Å c = 18.490 (3) Å

TABLE 5-continued

Crystallographic data of azithromycin form F.

	Form F
	α = 90° β = 109.33(1)° γ = 90°
Z (per formula)	4
Density (g/cm³)	1.13
R	0.0688

TABLE 6

Crystallographic data of azithromycin form G.

	Form G
Formula	$C_{38}H_{72}N_2O_{12}.1.5H_2O$
Formula weight	776.0
Crystal size (mm)	0.04 x 0.20 x 0.24
Space group	$P2_1$ monoclinic
Unit cell dimensions	a = 16.4069(8) Å b = 16.2922(6) Å c = 18.3830 (9) Å α = 90° β = 110.212(2)° γ = 90°
Z (per formula)	4
Density (g/cm³)	1.12
R	0.0785

TABLE 7

Crystallographic data of azithromycin form H.

	Form H
Empirical formula	$C_{38}H_{72}N_2O_{12}.H_2O.0.5C_2H_6O_2$
Crystal size (mm)	0.14 x 0.20 x 0.24
Formula weight	805.0
Space group	$P2_1$ monoclinic
Unit cell dimensions	a = 16.177 (1) Å b = 16.241 (2) Å c = 18.614 (1) Å α = 90° β = 108.34 (1)° γ = 90°
Z (per formula)	4
Density (g/cm³)	1.15
R	0.0687

TABLE 8

Crystallographic data of azithromycin form J.

	Form J
Formula	$C_{38}H_{72}N_2O_{12}.H_2O.0.5C_2H_6O$
Formula weight	796.0
Crystal size (mm)	0.40 x 0.36 x 0.20
Space group	$P2_1$ monoclinic
Unit cell dimensions	a = 16.191(6) Å b = 16.237(10) Å c = 18.595(14) Å α = 90° β = 108.92(4)° γ = 90°
Z (per formula)	4
Density (g/cm³)	1.14
R	0.0789

TABLE 8A

Crystallographic data of azithromycin form O.

	Form O
Formula	$C_{38}H_{72}N_2O_{12}\cdot 0.5H_2O\cdot 0.5C_6H_{10}O$
Formula weight	795.04
Crystal size (mm)	0.40 × 0.36 × 0.20
Space group	$P2_1$ monoclinic
Unit cell dimensions	a = 16.3602(11) Å b = 16.2042(11) Å c = 18.5459(12) Å α = 90° β = 109.66(10)° γ = 90°
Z (per formula)	4
Density (g/cm³)	1.14
R	0.0421

Among these sixteen crystal forms, two isomorphic families are identified. Family I includes forms F, G, H, J, M, N, O, and P. Family II includes forms C, D, E and R. Form Q is distinct from families I and II. The forms within a family are isomorphs that crystallize in the same space group with slight variation of cell parameters and comprise chemically related structures but different elemental composition. In this case, the variation in chemical composition among the isomorphs arises from incorporation of different water/solvent molecules. Consequently, the isomorphs display similar but non-identical X-ray diffraction patterns and solid-state NMR spectra (ssNMR). Other techniques such as near infrared spectroscopy (NIR), differential scanning calorimetry (DSC), gas chromatography (GC), thermalgravimetric analysis (TGA), or thermalgravimetric analysis/infrared spectroscopy analysis (TG-IR), Karl Fischer water analysis (KF) and molecular modeling/visualization provide data for affirmative identification of isomorphs. Dehydration/desolvation temperatures were determined by DSC with a heating rate of 5° C./min

Form C

This crystal form was identified from a single crystal structure (Table 2)—a monohydrate of azithromycin. It has the space group of $P2_12_12_1$, and similar cell parameters as that of forms D and E; therefore, it belongs to Family II isomorphs. Its calculated powder pattern is similar to that of forms D and E.

Form D

Form D was crystallized from cyclohexane. The single crystal structure of form D shows a stoichiometry of a monohydrate/monocyclohexane solvate of azithromycin (Table 3). Cyclohexane molecules were found to be disordered in the crystal lattice. From single crystal data, the calculated water and cyclohexane content of form D is 2.1 and 9.9%, respectively. Both the powder pattern and the calculated powder pattern of form D are similar to those of forms C and E. The powder samples of form D showed a desolvation/dehydration endotherm with an onset temperature of about 87° C. and a broad endotherm between 200–280° C. (decomposition) in DSC analysis at 5°C./min from 30–300° C.

Form D is prepared by slurrying azithromycin in cyclohexane for 2–4 days. The solid form D azithromycin is collected by filtration and dried.

Form E

Form E was obtained as a single crystal collected in a THF/water medium. It is a monohydrate and mono-THF solvate by single crystal analysis (Table 4). By its single crystal structure, the calculated PXRD pattern is similar to that of form C and form D making it a family II isomorph.

Form E is prepared by dissolving azithromycin in THF (tetrahydrofuran). Diffusing water vapor through saturated azithromycin THF solution over time yields crystals of Form E.

Form F

The single crystal of form F crystallized in a monoclinic space group, $P2_1$, with the asymmetric unit containing two azithromycin, two waters, and one ethanol, as a monohydrate/hemi-ethanolate (Table 5). It is isomorphic to all family I azithromycin crystalline forms. The calculated PXRD pattern of this form is similar to those of other family I isomorphs. The theoretical water and ethanol contents are 2.3 and 2.9%, respectively. The powder samples show a dehydration/desolvation endotherm at an onset temperature between 110–125° C. Form F is prepared by dissolving azithromycin in ethanol (1–3 volumes by weight) at a temperature of about 50–70° C. Upon complete dissolution, the solution is cooled to subambient temperature to cause precipitation. The volume of ethanol can be reduced by vacuum distillation with stirring for 1–2 hours to increase the yield. Alternatively, water (optionally chilled to 0–20° C.) about 0.1–2 volume can be added with collection of solids within 30 minute after water addition. Cooling the ethanol solution of azithromycin prior to the addition of water to below below 20° C., preferably below 15° C., more preferably below 10, and most preferably 5° C. results in substantially pure azithromycin form F. The solid form F azithromycin is collected by filtration and dried.

Form G

The single crystal structure of form G consists of two azithromycin molecules and three water molecules per asymmetric unit (Table 6). This corresponds to a sesquihydrate with a theoretical water content of 3.5%. The water content of powder samples of form G ranges from about 2.5 to about 6%. The total residual organic solvent is less than 1% of the corresponding solvent used for crystallization, which is well below stoichiometric quantities of solvate. This form dehydrates with an onset temperature of about 110–120° C.

Form G may be prepared by adding azithromycin to a premixed organic solvent/water mixture (1/1 by volume), where the organic solvent can be methanol, acetone, acetonitrile, ethanol or isopropanol. The mixture is stirred and heated to an elevated temperature, e.g. 45–55° C. for 4–6 hours to cause dissolution. Precipitation occurs during cooling to ambient temperature. The solid form G azithromycin is collected by filtration and dried.

Form H

This crystal form is a monohydrate/hemi-propylene glycol solvate of azithromycin free base (Table 7). It was isolated from a formulation solution containing propylene glycol. The crystal structure of form H is isomorphic to crystal forms of Family I.

Azithromycin form H is prepared by dissolving azithromycin dihydrate in 6 volumes of propylene glycol. To the resulting propylene glycol solution of azithromycin, 2 volumes of water is added and precipitation occurs. The slurry is stirred for 24 hours and the solids are filtered and air-dried at ambient temperature to afford crystalline Form H.

Form J

Form J is a monohydrate/hemi n-propanol solvate (Table 8). The calculated solvent content is about 3.8% n-propanol and about 2.3% water. The experimental data shows from about 2.5 to about 4.0% n-propanol and from about 2.5 to about 3% water content for powder samples. Its PXRD pattern is very similar to those of its isomorphs F, G, H, M and N. Like F and G, the powder samples have a dehydration/desolvation endotherm at 115–125° C.

Form J is prepared by dissolving azithromycin in 4 volumes of n-propanol at a temperature of about 25–55° C. Water, about 6–7 volumes, is added at room temperature and the slurry is continuously stirred for 0.5–2 hours. The solid form J azithromycin is collected by filtration and dried.

Form K

The PXRD pattern of form K was found in a mixture of azithromycin form A and microcrystalline wax after annealing at 95° C. for 3 hours. It is a lower hydrate of form A and is a metastable high temperature form.

Form L

This form has only been observed upon heating the dihydrate; form A. In variable temperature powder X-ray diffraction (VT-PXRD) experiments, a new powder X-ray diffraction pattern appears when form A is heated to about 90° C. The new form, designated form L, is a lower hydrate of form A because form A loses about 2.5 weight % at 90° C. by TGA, thus corresponding to a conversion to a monohydrate. When cooled to ambient temperature, form L rapidly reverts to form A.

Form M

Isolated from an isopropanol/water slurry, form M incorporates both water and isopropanol. Its PXRD pattern and ss-NMR spectrum are very similar to those of Family I isomorphs, indicating that it belongs to Family I. By analogy to the known crystal structures of Family I isomorphs, the single crystal structure of form M would be a monohydrate/hemi-isopropranolate. The dehydration/desolvation temperature of form M is about 115–125° C.

Form M may be prepared by dissolving azithromycin in 2–3 volumes of isopropanol (IPA) at 40–50° C. The solution is cooled to below 15° C., preferably below 10° C., more preferably about 5° C. and 2–4 volumes of cold water about 5° C. are added to effect precipitation. Seeds of form M crystals may be added at the onset of crystallization. The slurry is stirred less than about 5 hours, preferably less than about 3 hours, more preferably less than about 1 hour and most preferably about 30 minutes or less and the solids are collected by filtration. The solids may be reslurried in isopropanol. This procedure provides form M substantially in the absence of azithromycin dihydrate.

Form N

Isolated from water/ethanol/isopropanol slurry of form A, form N crystals may contain variable amounts of the crystallization solvents and water. Its water content varies from about 3.4 to about 5.3 weight percent. Analysis by GC Headspace reveals a variable solvent content of ethanol and isopropanol. The total solvent content of form N samples is usually lower than about 5% depending on the conditions of preparation and drying. The PXRD pattern of form N is similar to that of forms F, G, H, J and M of the Family I isomorphs. The dehydration/desolvation endotherm(s) of the samples of form N may be broader and may vary between 110–130° C.

Form N azithromycin may be prepared by recrystallizing azithromycin from a mixture of azithromycin crystal lattice-incorporating organic solvents and water, such as ethanol, isopropanol, n-propanol, acetone, acetonitrile etc. The solvent mixture is heated to 45–60° C. and azithromycin is added to the heated solvent mixture, up to a total of about 4 volumes. Upon dissolution, 1–3 volumes of water are added with continuous agitation at 45–60° C. Form N azithromycin precipitates as a white solid. The slurry is allowed to cool to ambient temperature with stirring. Solid form N azithromycin is isolated by filtration and dried.

Form O

This crystal form is a hemihydrate hemi-n-butanol solvate of azithromycin free base by single crystal structural data (Table 8A). It was isolated from n-butanol solution of azithromycin with diffusion of antisolvent. The crystal structure of form O is isomorphic to crystal forms of Family I.

Azithromycin is completely dissolved in n-butanol. Addition of an antisolvent, such as hexane, water, IPE or other non-solvent, by diffusion results in precipitation of Form O.

Form P

This is a proposed crystal form, being a hemihydrate hemi-n-pentanol solvate of azithromycin free base. It can be isolated from an n-pentanol solution of azithromycin with diffusion of an antisolvent. The crystal structure of form P is isomorphic to crystal forms of Family I.

Form P of azithromycin may be prepared as following: Azithromycin is completely dissolved in n-pentanol; addition of an antisolvent, such as hexane, water, isopropyl ether (IPE) or other non-solvent, by diffusion results in precipitation of Form P.

Form Q

The crystal form of Q exhibits a unique powder X-ray diffraction pattern. It contains about 4% water and about 4.5% THF, being a hydrate hemi THF solvate. The main dehydration/desolvation temperature is from about 80 to about 110° C.

Azithromycin dihydrate is dissolved in 6 volumes of THF and 2 volumes of water are added. The solution is allowed to evaporate to dryness at ambient conditions to afford crystalline Form Q.

Form R

This crystalline form is prepared by adding amorphous azithromycin to 2.5 volumes of tert-butyl methyl ether (MTBE). The resulting thick white suspension is stirred 3 days at ambient conditions. Solids are collected by vacuum filtration and air dried. The resulting bulk azithromycin form R has a theoretical water content of 2.1 weight % and a theoretical methyl tert-butyl ether content of 10.3 weight %.

Due to the similarity in their structures, isomorphs have propensity to form a mixture of the forms within a family, sometimes termed as 'mixed crystals' or 'crystalline solid solution'. Form N is such a solid crystalline solution and was found to be a mixture of Family I isomorphs by solvent composition and solid-state NMR data.

Both Family I and Family II isomorphs are hydrates and/or solvates of azithromycin. The solvent molecules in the cavities have tendency to exchange between solvent and water under specific conditions. Therefore, the solvent/water content of the isomorphs may vary to a certain extent.

The crystal forms of isomorphic Family I are more stable than form A when subjected to heating. Forms F, G, H, J, M and N showed higher onset dehydration temperatures at 110–125° C. 110–125° C. than that of form A with an onset dehydration temperature at about 90 to about 110° C. and simultaneous solid-state conversion to form L at about 90° C.

Amorphous Azithromycin

All crystal forms of azithromycin contain water or solvent(s) or both water and solvent(s). When water and solvent(s) are removed from the crystalline solids, azithromycin becomes amorphous. Amorphous solids have advantages of high initial dissolution rates.

The starting material for the synthesis of the various crystal forms in the examples below was azithromycin dihydrate unless otherwise noted. Other forms of azithromycin such as amorphous azithromycin or other non-dihydrate crystalline forms of azithromycin may be used.

EXAMPLES

Example 1

Preparation of Form D

Form D was prepared by slurrying azithromycin dihydrate in cyclohexane for 2–4 days at an elevated temperature, e.g.

25–50° C. The crystalline solids of form D were collected by filtration and dried.

Example 2

Preparation of Form F

2A;

Azithromycin dihydrate was slowly added to one volume of warm ethanol, about 70° C., and stirred to complete dissolution at 65 to 70° C. The solution was allowed to cool gradually to 2–5° C. and one volume of chilled water was added The crystalline solids were collected shortly (preferably less than 30 minutes) after addition of water by vacuum filtration.

2B;

Azithromycin dihydrate is slowly added to one volume of warm ethanol, about 70° C., and stirred to complete dissolution at 65 to 70° C. The solution is allowed to cool gradually to 2–5° C. and ethanol volume may be reduced by vacuum distillation. Seeds of Form F 1–2% wt may be introduced to facilitate the crystallization. After stirring up to 2 hours the crystalline solids are collected by vacuum filtration. The isolation of the crystals yields substantially pure form F azithromycin, form F azithromycin substantially free of form G azithromycin and form F azithromycin substantially free of azithromycin dihydrate.

Example 3

Preparation of Form G

A reaction vessel was charged with form A azithromycin. In a separate vessel, 1.5 volumes methanol and 1.5 volumes water were mixed. The solvent mixture was added to the reaction vessel containing the form A azithromycin. The slurry was stirred with heating to 50° C. for approximately 5 hours. Heating was discontinued and the slurry was allowed to cool with stirring to ambient temperature. The form G azithromycin was collected by filtration and allowed to air dry for approximately 30 minutes. The collected form G azithromycin was further dried in a vacuum oven at 45° C. This procedure yields substantially pure form G azithromycin, and form G azithromycin substantially free of azithromycin dihydrate.

Example 4

Preparation of Form J

Form J was prepared by dissolving azithromycin in 4 volumes of n-propanol at a temperature of about 25° C. Water (6.7 volumes) was added and the slurry is continuously stirred for 1 hour, followed by cooling to about 0° C. The solid form J azithromycin was collected by filtration and dried.

Example 5

Preparation of Form M Substantially in the Absence of Azithromycin Dihydrate

5A;

Azithromycin dihydrate is completely dissolved in 2 volumes of warm isopropanol 40–50° C. Seeds of Form M may be optionally introduced to facilitate the crystallization. The solution is then cooled to 0–5° C. and 4 volumes of chilled water as antisolvent are added and the solids are collected by vacuum filtration. The solids are reslurried in 1 volume of isopropanol for 3–5 hours at 40–45° C. and then cooled to 0–5° C. The crystalline solids are collected shortly

(about 15 minutes) after addition of water by vacuum filtration. The solids are reslurried in 0.5 to 1 volume of isopropanol at 25–40° C. and cooled to about 5° C. followed by filtration to collect solids of form M.

These procedures yield substantially pure form M azithromycin, form M azithromycin substantially free of form G azithromycin and form M azithromycin substantially free of azithromycin dihydrate

Example 6

Preparation of Form N

Two volumes of ethanol and 2 volumes of isopropanol were added to a reaction vessel and heated to 50° C. Azithromycin form A was added with stirring to the heated ethanol/isopropanol mixture to yield a clear solution. The reaction vessel was charged with 2 volumes distilled water (ambient temperature). Stirring was continued at 50° C. and solid form N azithromycin precipitated after approximately 1 hr. Heating was discontinued 5 hours after the addition of the water. The slurry was allowed to cool to ambient temperature. Precipitated form N azithromycin was collected by filtration and dried for 4 hours in vacuum oven at 45° C.

Example 7

Preparation of Amorphous Azithromycin

Crystalline form A azithromycin was heated to 110–120° C. in an oven for overnight under vacuum. The amorphous solids were collected and stored with desiccant as needed.

Example 8

Preparation of Form H

Azithromycin dihydrate or other crystal forms was dissolved in 6 volumes of propylene glycol. To the resulting propylene glycol solution of azithromycin, 2 volumes of water were added and precipitation occurred. The slurry was stirred for 24 hours and the solids were filtered and air-dried at ambient temperature to afford crystalline Form H.

Example 9

Preparation of Form Q

The crystalline powder was prepared by dissolving 500 mg azithromycin Form A in 2 ml THF. To the clear, colorless solution at room temperature was added 1 ml water. When the solution became cloudy an additional 1 ml THF was added to dissolve the azithromycin completely, and the solution was stirred at ambient temperature. Solvent was allowed to evaporate over 7 days, after which the dry solids were collected and characterized.

Example 10

Powder X-ray Diffraction Analysis

Powder patterns were collected using a Bruker D5000 diffractometer (Madison, Wis.) equipped with copper radiation, fixed slits (1.0, 1.0, 0.6 mm), and a Kevex solid state detector. Data was collected from 3.0 to 40.0 degrees in 2 theta using a step size of 0.04 degrees and a step time of 1.0 seconds. The results are summarized in Table 9.

The experimental PXRD diffraction pattern of azithromycin form A is given in FIG. 2.

The experimental PXRD diffraction pattern of azithromycin form D is given in FIG. 6.

The experimental PXRD diffraction pattern of azithromycin form F is given in FIG. 10.

The experimental PXRD diffraction pattern of azithromycin form G is given in FIG. 13.

The experimental PXRD diffraction pattern of azithromycin form J is given in FIG. 16.

The experimental PXRD diffraction pattern of azithromycin form M is given in FIG. 18.

The experimental PXRD diffraction pattern of azithromycin form N is given in FIG. 19.

The experimental PXRD diffraction pattern of amorphous azithromycin is given in FIG. 20.

The experimental PXRD diffraction pattern of azithromycin form Q is given in FIG. 30.

The experimental PXRD diffraction pattern of azithromycin form R is given in FIG. 31.

The experimental variability from sample to sample is about ±0.2° in 2 theta, and the same variations were observed between the calculated powder from single crystal structure and experimental data. Detailed analysis showed that the isomorphs in Family I can be discerned by PXRD with sets of characteristic peaks given in Table 9.

TABLE 9

Azithromycin Powder X-ray Diffraction Peaks in 2-theta ±0.2°

A	D	F	G	J	M	N	Q
7.2	3.9	5.7	5.0	5.0	5.0	6.2	5.7
7.9	7.3	6.2	5.8	5.7	5.6	7.3	6.1
9.3	7.7	7.4	6.2	6.2	6.2	7.8	6.8
9.9	10.1	7.8	7.4	7.3	7.3	9.8	8.4
11.2	10.6	8.9	7.9	7.8	7.8	*11.2*	9.5
12.0	11.5	*9.8*	9.8	8.2	8.2	11.9	10.6
12.7	12.3	10.3	10.2	9.7	9.8	12.5	11.2
13.0	12.8	*11.2*	10.8	10.3	10.2	*14.0*	11.5
14.0	13.6	*11.5*	*11.2*	*11.2*	*11.2*	*14.3*	12.4
15.6	14.5	11.9	*11.6*	*11.4*	11.9	*14.7*	12.7
16.0	15.4	12.2	12.0	11.9	12.2	15.3	13.4
16.4	15.6	12.5	12.5	12.3	12.5	15.7	13.6
16.8	16.9	*13.9*	13.3	12.5	*14.0*	*16.1*	14.1
17.5	18.3	*14.3*	*14.0*	*13.9*	*14.6*	*16.6*	14.4
18.2	19.0	*14.7*	*14.4*	*14.2*	15.3	*17.1*	14.9
18.7	19.9	*14.8*	*14.6*	*14.6*	*15.9*	*17.4*	16.3
19.1	20.8	15.3	*14.9*	15.3	*16.6*	18.5	17.2
19.8	21.4	15.7	15.3	15.7	*17.1*	19.0	18.2
20.5	21.6	*16.2*	15.7	*16.0*	*17.5*	19.6	19.0
20.9	22.0	*16.6*	*16.1*	*16.6*	18.4	20.0	19.5
21.2	23.0	*17.1*	*16.6*	*17.0*	18.5	20.4	19.8
21.6	23.3	*17.2*	*17.2*	*17.2*	19.1	*21.0*	*20.2*
21.8		*17.7*	*17.4*	*17.5*	19.6	21.8	20.5
24.0		18.0	*17.8*	18.1	20.0	*22.5*	21.1
		18.5	18.1	18.5	20.4	23.5	21.6
		19.0	18.6	19.0	*20.9*		21.9
		19.6	19.0	19.7	21.7		22.2
		20.0	19.6	20.0	*22.5*		23.6
		20.5	20.0	20.4	23.2		25.1
		21.0	20.5	*20.9*	23.6		
		21.7	*21.1*	21.7			
		22.0	21.8	22.4			
		22.4	*22.5*	*22.6*			
		22.6	23.5	23.3			
		23.1		23.5			
		23.5					

The peaks underlined are the characteristic peaks among forms A, D, Family I and Q.
The peaks in italic and underlined are the sets of peaks that are characteristic within Family I isomorphs.

Family I isomorphs have the following common characteristics: the diffraction peaks at 6.2, 11.2, 21.0±0.1 and 22.5±0.1 degree in 2-theta. Each isomorph displays representative sets of diffraction peaks given in the following, and each set has characteristic spacing between the peaks.

The diffraction peak positions reported are accurate to within ±0.2 degree of 2-theta.

A representative PXRD pattern of form A is shown in FIG. 2. Form A displays peaks at 9.3, 13.0 and 18.7 degrees of 2-theta.

A representative PXRD pattern of form D is shown in FIG. 6. Form D displays peaks at 3.9, 10.1, 10.6 and 21.4 degrees of 2-theta.

A representative PXRD pattern of Form F is shown in FIG. 10. Form F displays the characteristic peaks of Family I and three sets of peaks, being set 1 at 2-theta of 11.2 and 11.5; set 2 at 2-theta of 13.9, 14.3, 14.7 and 14.8; set 3 at 2-theta of 16.2, 16.6, 17.1, 17.2 and 17.7.

A representative PXRD pattern of Form G is shown in FIG. 13. Form G displays the characteristic peaks of Family I and three sets of peaks, being set 1 at 2-theta of 11.2 and 11.6 2; set at 2-theta of 14.0, 14.4, 14.6 and 14.9; set 3 at 2-theta of 16.3, 16.6, 17.2, 17.4 and 17.8.

A representative PXRD pattern of Form J is shown in FIG. 16. Form J displays the characteristic peaks of Family I and three sets of peaks, being set 1 at 2-theta of 11.2 and 11.4; set 2 at 2-theta of 13.9, 14.2 and 14.6; set 3 at 2-theta of 16.0, 16.6, 17.0, 17.2 and 17.5.

A representative PXRD pattern of Form M is shown in FIG. 18. Form M displays the characteristic peaks of Family I and three sets of peaks, being set 1 at 2-theta of 11.2; set 2 at 2-theta of 14.0 and 14.6; set 3 at 2-theta of 15.9, 16.6, 17.1 and 17.5.

A representative PXRD pattern of Form N is shown in FIG. 10. Form N displays the characteristic peaks of Family I. The sets of peaks of form N are similar to those of forms F, G, J and M, being set 1 at 2-theta of 11.2 to 11.6; set 2 at 2-theta of 13.9 to 15.0; and set 3 at 2-theta of 15.9 to 17.9, with the peaks may vary slightly in position, intensity and width due to mixing of variable proportion of isomorphs in Family I.

A representative PXRD pattern of form Q is shown in FIG. 30. Form Q displays peaks at 2-theta of 6.8, 8.4 and 20.2 degree.

A representative PXRD pattern of form R is shown in FIG. 31.

Example 11

Single Crystal X-ray Analysis

Data were collected at room temperature using Bruker X-ray diffractometers equipped with copper radiation and graphite monochromators. Structures were solved using direct methods. The SHELXTL computer library provided by Bruker AXS, Inc facilitated all necessary crystallographic computations and molecular displays (SHELXTL™ Reference Manual, Version 5.1, Bruker AXS, Madison, Wis., U.S.A. (1997)).

Example 12

Calculation of PXRD Pattern from Single Crystal Data

To compare the results between a single crystal and a powder sample, a calculated powder pattern can be obtained from single crystal results. The XFOG and XPOW computer programs provided as part of the SHELXTL computer library were used to perform this calculation. Comparing the calculated powder pattern with the experimental powder pattern confirms whether a powder sample corresponds to an

assigned single crystal structure (Table 9A). This procedure was performed on the crystal forms of azithromycin A, D, F, G, and J.

The calculated PXRD diffraction pattern of azithromycin form A is given in FIG. 1.

The calculated PXRD diffraction pattern of azithromycin form D is given in FIG. 5.

The calculated PXRD diffraction pattern of azithromycin form F is given in FIG. 9.

The calculated PXRD diffraction pattern of azithromycin form G is given in FIG. 12.

The calculated PXRD diffraction pattern of azithromycin form J is given in FIG. 15.

The results are displayed in the overlaid powder X-ray diffraction patterns for forms A, D, F, G, and J in FIGS. 3, 7, 11, 14 and 17, respectively. The lower pattern corresponds to the calculated powder pattern (from single crystal results) and the upper pattern corresponds to a representative experimental powder pattern. A match between the two patterns indicated the agreement between powder sample and the corresponding single crystal structure.

TABLE 9A

Calculated and Experimental PXRD Peaks of Isomorphs of Family I

F calculated	F experimental	G calculated	G experimental	J calculated	J experimental	M experimental
		5.2	5.0			
		5.7	5.8	5.8	5.7	5.6
6.3	6.2	6.2	6.2	6.3	6.2	6.2
7.4	7.4	7.5	7.4	7.4	7.3	7.3
7.9	7.8	7.9	7.9	7.9	7.8	7.8
8.8	8.9	8.9	9.3	8.3	8.2	8.2
9.9	9.8	9.9	9.9	9.8	9.7	9.8
10.3	10.3		10.2	10.4	10.3	10.2
10.9		10.9	10.8			
11.3	11.2	11.3	11.2	11.2	11.2	11.2
11.5	11.4	11.6	11.6	11.4	11.4	missing
12.0	11.9	12.0	11.9	12.0	11.9	11.9
12.3	12.2	12.3		12.3	12.3	12.2
12.6	12.5	12.5	12.5	12.6	12.5	12.5
14.0	14.0	13.4	13.3	14.0	13.9	14.0
14.3	14.3	14.1	14.0	14.2	14.2	missing
		14.4	14.4			
14.7	14.7	14.7	14.6	14.7	14.6	14.6
14.9	14.8	14.9	14.9	14.8		
15.4	15.3	15.4	15.3	15.3	15.3	15.3
15.8	15.7	15.7	15.7	15.8	15.7	15.9
16.2	16.2	16.3	16.3	16.0	16.0	missing
16.6	16.6	16.6	16.6	16.7	16.6	16.6
17.1	17.2	17.1		17.1	17.0	17.1
17.3	17.3	17.3	17.2	17.4	17.2	missing
17.5	17.4	17.5	17.4	17.6	17.5	17.5
17.7	17.7	17.9	17.8	17.9		
18.0	18.0	18.1	18.1	18.2	18.1	18.4

TABLE 9A-continued

Calculated and Experimental PXRD Peaks of Isomorphs of Family I

F calculated	F experimental	G calculated	G experimental	J calculated	J experimental	M experimental
18.6	18.5	18.7	18.7	18.5	18.5	18.5
19.1	19.0	19.1	19.0	19.1	19.0	19.1
19.7	19.6	19.6	19.6	19.8	19.7	19.6
20.0	20.0	20.0	20.0	20.1	20.0	20.0
20.5	20.4	20.6	20.5	20.5	20.4	20.4
21.1	21.0	21.2	21.0	20.8	20.9	20.9
21.8	21.7		21.6	21.6	21.7	21.7
22.1	22.0	21.8	21.8	21.8		
22.5	22.4	22.3	22.2	22.5	22.4	22.5
22.7	22.6	22.5	22.5	22.8	22.6	
23.1	23.1	22.9		23.4	23.3	23.2
23.6	23.5	23.5	23.5	23.7	23.5	23.6

Example 13

Solid State NMR Analysis

Solid State NMR Analysis

All ^{13}C solid state NMR spectra were collected on an 11.75 T spectrometer (Bruker Biospin, Inc., Billerica, Mass.), corresponding to 125 MHz ^{13}C frequency. The spectra were collected using a cross-polarization magic angle spinning (CPMAS) probe operating at ambient temperature and pressure. Depending on the quantity of sample analyzed, 7 mm BL or 4 mm BL Bruker probes were employed, accomodating 300 mg and 75 mg of sample with maximum speeds of 7 kHz and 15 kHz, respectively. Data were processed with an exponential line broadening function of 5.0 Hz. Proton decoupling of 65 kHz and 100 kHz were used with the 7 mm and 4 mm probes, respectively. A sufficient number of acquisitions were averaged out to obtain adequate signal-to-noise ratios for all peaks. Typically, 600 scans were acquired with recycle delay of 3.0 s (seconds), corresponding approximately to a 30 minute total acquisition time. Magic angle was adjusted using KBr powder according to standard NMR vendor practices. The spectra were referenced relative to either the methyl resonance of hexamethylbenzen (HMB) at 17.3 ppm or the upfield resonance of adamantane (ADM) at 29.5 ppm. HMB referenced spectra show chemical shifts of all peaks shifted down field by 0.08 ppm with respect to same spectra referenced to ADM. The spectral window minimally included the spectra region from 190 to 0 ppm. The results are summarized in Table 10. Ss-NMR spectra for forms M, H and R were referenced to ADM. Ss-NMR spectra for forms A, D, G, F, J and N were referenced to HMB. Forms H and R were spun at a rate of 15 kHz.

TABLE 10

^{13}C ss-NMR chemical shifts of Azithromycin (±0.2 ppm)

A	D	G	F	J	M	N	H	R
178.1	178.1	179.5*	179.5	179.6	179.6	179.6	179.5	177.9
104.1	103.9	105.5	178.6	178.4	105.6	178.7	178.7	104.6
98.4	95.1	103.5	105.5	105.5	103.4	105.6	105.4	103.6
84.6	84.2	95.0	103.4	103.4	94.9	103.6	103.2	95.1
82.6	79.4	86.2	94.9	95.0	86.7	95.0	95.0	85.4
79.3	78.9	83.1	86.4	86.4	82.9	86.5	86.4	84.0

TABLE 10-continued

^{13}C ss-NMR chemical shifts of Azithromycin (±0.2 ppm)

A	D	G	F	J	M	N	H	R
78.3	75.7	78.9	83.0.	82.9	79.3	83.1	82.7	79.4
75.6	74.6	78.2	79.1	79.2	78.1	79.0	79.2	79.0
74.7	74.0	77.6	78.1	78.1	77.0	77.9	78.3	75.6
73.9	72.9	76.4	77.9	76.8	76.7	76.5	78.0	74.5
73.5	71.9	75.7	76.5	76.2	74.7	74.8	76.4	73.9
70.8	71.0	74.7	74.7	74.7	74.2	74.2	74.7	73.9
68.0	69.4	74.3	74.1	74.1**	71.3	73.6	74.1	72.9
66.2	67.8	73.5	73.5	72.0	69.2	71.5	73.5	71.8
63.8	65.7	71.3	71.4	71.3	68.6	69.2	73.1	71.0
63.2	64.7	69.1	69.1	69.2	67.3	68.7	71.2	69.1
52.2	49.2	68.8	68.6	68.6	66.2	67.3	69.1	67.5
44.3	45.8	67.4	67.3	67.3**	65.5	66.2	68.4	65.6
42.6	43.1	65.9	66.1	66.2**	63.8	65.7	67.3	64.5
41.7	40.6	65.2	65.6	65.5**	63.3	63.7	66.9	49.4
39.1	37.1	64.0	63.6	63.7	50.0	*58.1*	66.1	45.7
35.4	36.4	63.3	**58.0**	50.0	47.1	50.1	65.5*	42.9
34.6	29.6	50.0	50.0	46.9	45.9	47.1	63.7*	41.6
26.9	29.3	46.9	47.0	45.9	44.7	46.0	49.9	40.4
26.3	28.0	46.0	45.9	44.7	43.8	44.8	46.8	37.0
23.7	27.7	44.5	44.7	43.7	41.9	43.8	45.9	36.2
23.3	22.1	43.7	43.7	41.6	41.1	41.5	44.5	29.4
21.7	21.1	41.5	41.5	41.0	37.4	41.1	43.8*	29.0
19.5	18.6	40.8	41.1	37.1	36.2	37.3	41.7	28.2
17.5	16.7	37.5	37.3	36.5**	33.6	36.5	40.9	27.4
15.9	16.1	36.5	36.4	35.4**	30.1	33.7	37.1	21.4
13.2	**10.6**	33.6	33.6	33.5	28.1	30.4	36.3	20.8
11.3	**9.0**	30.0	30.3	30.4	27.2	28.1	33.7	18.7
7.2	**8.6**	27.9	28.0	28.0	**26.0**	27.2	33.3	16.5
		27.3	27.1	27.1	23.2	**26.0**	30.5*	16.1
		23.1	23.2	**25.2**	22.8	23.2	27.9	15.7
		23.5	22.6	23.2	22.5	22.6	27.1	**10.3**
		21.9	21.9	22.5**	21.8	22.0	23.1	**9.6**
		20.9	20.8	21.9**	20.2	20.8	22.6	**8.9**
		20.2	20.4	20.7	18.9	19.0	22.3	**8.6**
		18.8	18.9	18.9	17.4	16.9	21.9	
		17.0	16.8	16.8	16.3	15.8	20.7	
		16.0	**17.2**	15.6**	15.5	12.2	20.3	
		12.2	15.7	12.1	12.1	**9.9**	18.8	
		10.4	12.2	*11.5*	**10.3**	**9.4**	17.1	
		9.9	**10.1**	12.1	**9.6**	**7.9**	16.6	
		9.3	**9.8**	**10.0**	**9.3**	**6.6**	15.8	
		7.6	**9.3**	**9.3**	**7.7**		15.4	
		6.5	**7.9**	**8.1**	**7.1**		12.0	
			6.6	**6.8****			**9.9**	
							9.1	
							7.9	
							7.0	

The chemical shifts labeled in bold and underlined are the peaks or sets of peaks representative of each form. The chemical shifts labeled in italic are the solvent peaks that may be broad and variable (±0.4 ppm). The chemical shifts labeled with single asterisk may show splitting of <0.3 ppm. The chemical shifts labeled with double asterisks may show variation of ±0.3 ppm.

The chemical shifts reported are accurate to within ±0.2 ppm unless otherwise indicated.

A representative ^{13}C ssNMR spectrum of form A is shown in FIG. 21. Form A displays a peak at 178.1 ppm, and peaks at 104.1, 98.4, 84.6, 26.9, 13.2, 11.3 and 7.2 ppm.

A representative ^{13}C ssNMR spectrum of form D is shown in FIG. 22. Form D displays the highest chemical shift peak of 178.1 ppm and peaks at chemical shifts of 103.9, 95.1, 84.2, 10.6, 9.0 and 8.6 ppm.

A representative ^{13}C ssNMR spectrum of form F is shown in FIG. 23. Form F has two chemical shift peaks at approximately 179.1±2 ppm, being 179.5 ppm and 178.6 ppm, and a set of 5 peaks at 10.1, 9.8, 9.3, 7.9, and 6.6 ppm, and ethanol peaks at 58.0±0.5 ppm and 17.2±0.5 ppm. The solvent peaks can be broad and relatively weak in intensity.

A representative ^{13}C ssNMR spectrum of form G is shown in FIG. 24. Form G has the highest chemical shift peak of 179.5 ppm, being a single peak with possible splitting of <0.3 ppm and a set of 5 peaks at 10.4, 9.9, 9.3, 7.6, 6.5 ppm.

A representative ^{13}C ssNMR spectrum of form J is shown in FIG. 25. Form J has two chemical shift peaks at approximately 179.1±2 ppm, those being 179.6 ppm and 178.4 ppm, a set of 4 peaks at 10.0, 9.3, 8.1 and 6.8 ppm and n-propanol peaks at 11.5±0.5 ppm and 25.2±0.5 ppm. The solvent peak can be broad and relatively weak in intensity.

A representative ^{13}C ssNMR spectrum of form M is shown in FIG. 26. Form M has one chemical shift peak at 179±1 ppm, being 179.6 ppm, peaks at 41.9, and 16.3 ppm, a set of 5 peaks at 10.3, 9.6, 9.3, 7.7 and 7.1 ppm and an isopropanol peak at 26.0±0.5 ppm. The solvent peak can be broad and relatively weak in intensity.

A representative ^{13}C ssNMR spectrum of form N is shown in FIG. 27. Form N displays chemical shifts as a

combination of isomorphs in Family I. The peaks may vary in chemical shift and in relative intensities and width due to the mixing of variable proportion of isomorphs contained in the form N crystalline solid solution.

A representative ^{13}C ssNMR spectrum of amorphous form is shown in FIG. 28. The amorphous azithromycin displays broad chemical shifts. The characteristic chemical shifts have the peak positions at 179 and 11±0.5 ppm.

A summary of the observed ssNMR peaks for forms A, D, F, G, H, J, M, N and R azithromycin is given in Table 10.

Example 14

NMR Analysis of a Dosage Form

To demonstrate the ability of ^{13}C ssNMR to identify the form of azithromycin contained in a pharmaceutical dosage form, coated azithromycin tablets containing form G azithromycin were prepared and analyzed by ^{13}C ssNMR. Tablets were wet granulated and tabletted on an F-Press (Manesty, Liverpool, UK) using 0.262"x0.531" tooling. Tablets were formulated and tabletted to contain 250 mg of form G azithromycin with a total tablet weight of 450 mg using the formula given below. The tablets were uniformly coated with pink Opadry II® (mixture of lactose monohydrate, hydroxypropylmethylcellulose, titanium dioxide, Drug & Cosmetic red #30, and triacetin) (Colorcon, West Point, Pa.).

Material	Percentage	Batch(g)
Azithromycin form "G"	58.23	174.69
Pregelatinized corn starch	6.00	18.00
Anhydrous dicalcium phosphate	30.85	92.55
Sodium croscarmelose	2.00	6.00
Magnesium stearate with 10% sodium lauryl sulfate	2.92	8.76
Total	100.00	300.00

A coated tablet was gently crushed and the powdered sample was packed with a packing tool in solid state rotor containing no ^{13}C background. Analysis of the sample was performed under conditions outlined in Example 13.

A representative ^{13}C ssNMR spectrum of the tablet containing form G azithromycin is given in FIG. 29.

Example 15

Antimicrobial Activity

The activity of the crystal forms of the present invention against bacterial and protozoa pathogens is demonstrated by the compound's ability to inhibit growth of defined strains of human (Assay I) or animal (Assays II and II) pathogens.

Assay I

Assay I, described below, employs conventional methodology and interpretation criteria and is designed to provide direction for chemical modifications that may lead to compounds that circumvent defined mechanisms of macrolide resistance. In Assay I, a panel of bacterial strains is assembled to include a variety of target pathogenic species, including representatives of macrolide resistance mechanisms that have been characterized. Use of this panel enables the chemical structure/activity relationship to be determined with respect to potency, spectrum of activity, and structural elements or modifications that may be necessary to obviate resistance mechanisms. Bacterial pathogens that comprise the screening panel are shown in the table below. In many cases, both the macrolide-susceptible parent strain and the macrolide-resistant strain derived from it are available to provide a more accurate assessment of the compound's ability to circumvent the resistance mechanism. Strains that contain the gene with the designation of ermA/ermB/ermC are resistant to macrolides, lincosamides, and streptogramin B antibiotics due to modifications (methylation) of 23S rRNA molecules by an Erm methylase, thereby generally prevent the binding of all three structural classes. Two types of macrolide efflux have been described; msrA encodes a component of an efflux system in staphylococci that prevents the entry of macrolides and streptogramins while mefA/E encodes a transmembrane protein that appears to efflux only macrolides. Inactivation of macrolide antibiotics can occur and can be mediated by either a phosphorylation of the 2'-hydroxyl (mph) or by cleavage of the macrocyclic lactone (esterase). The strains may be characterized using conventional polymerase chain reaction (PCR) technology and/or by sequencing the resistance determinant. The use of PCR technology in this application is described in J. Sutcliffe et al., "Detection Of Erythromycin-Resistant Determinants By PCR", Antimicrobial Agents and Chemotherapy, 40(11), 2562–2566 (1996). The assay is performed in microtiter trays and interpreted according to *Performance Standards for Antimicrobial Disk Susceptibility Tests—Sixth Edition; Approved Standard*, published by The National Committee for Clinical Laboratory Standards (NCCLS) guidelines; the minimum inhibitory concentration (MIC) is used to compare strains. The crystalline compound is initially dissolved in dimethylsulfoxide (DMSO) as 40 mg/ml stock solution.

Strain Designation	Macrolide Resistance Mechanism(s)
Staphylococcus aureus 1116	susceptible parent
Staphylococcus aureus 1117	ErmB
Staphylococcus aureus 0052	susceptible parent
Staphylococcus aureus 1120	ErmC
Staphylococcus aureus 1032	msrA, mph, esterase
Staphylococcus hemolyticus 1006	msrA, mph
Streptococcus pyogenes 0203	susceptible parent
Streptococcus pyogenes 1079	ErmB
Streptococcus pyogenes 1062	susceptible parent
Streptococcus pyogenes 1061	ErmB
Streptococcus pyogenes 1064	ErmB
Streptococcus agalactiae 1024	susceptible parent
Streptococcus agalactiae 1023	ErmB
Streptococcus pneumoniae 1016	Susceptible
Streptococcus pneumoniae 1048	ErmB
Streptococcus pneumoniae 1095	ErmB
Streptococcus pneumoniae 1175	MefE
Streptococcus pneumoniae 0085	Susceptible
Haemophilus influenzae 0131	Susceptible
Moraxella catarrhalis 0040	Susceptible
Moraxella catarrhalis 1055	erythromycin intermediate resistance
Escherichia coli 0266	Susceptible

Assay II is utilized to test for activity against *Pasteurella multocida* and Assay III is utilized to test for activity against *Pasteurella haemolytica*.

Assay II

This assay is based on the liquid dilution method in microliter format. A single colony of *P. multocida* (strain 59A067) is inoculated into 5 ml of brain heart infusion (BHI) broth. The test compound is prepared by solubilizing

1 mg of the compound in 125 μl of dimethylsulfoxide (DMSO). Dilutions of the test compound are prepared using uninoculated BHI broth. The concentrations of the test compound used range from 200 μg/ml to 0.098 μg/ml by two-fold serial dilutions. The *P. multocida* inoculated BHI is diluted with uninoculated BHI broth to make a 10^4 cell suspension per 200 μl. The BHI cell suspensions are mixed with respective serial dilutions of the test compound, and incubated at 37° C. for 18 hours. The minimum inhibitory concentration (MIC) is equal to the concentration of the compound exhibiting 100% inhibition of growth of *P. multocida* as determined by comparison with an uninoculated control.

Assay III

This assay is based on the agar dilution method using a Steers Replicator. Two to five colonies isolated from an agar plate are inoculated into BHI broth and incubated overnight at 37° C. with shaking (200 rpm). The next morning, 300 μl of the fully grown *P. haemolytica* preculture is inoculated into 3 ml of fresh BHI broth and is incubated at 37° C. with shaking (200 rpm). The appropriate amounts of the test compounds are dissolved in ethanol and a series of two-fold serial dilutions are prepared. Two ml of the respective serial dilution is mixed with 18 ml of molten BHI agar and solidified. When the inoculated *P. haemolytica* culture reaches 0.5 McFarland standard density, about 5 μl of the *P. haemolytica* culture is inoculated onto BHI agar plates containing the various concentrations of the test compound using a Steers Replicator and incubated for 18 hours at 37° C. Initial concentrations of the test compound range from 100–200 μg/ml. The MIC is equal to the concentration of the test compound exhibiting 100% inhibition of growth of *P. haemolytica* as determined by comparison with an uninoculated control.

The in vivo activity of the crystal forms of the present invention can be determined by conventional animal protection studies well known to those skilled in the art, usually carried out in mice.

Mice are allotted to cages (10 per cage) upon their arrival, and allowed to acclimate for a minimum of 48 hours before being used. Animals are inoculated with 0.5 ml of a 3×10^3 CFU/ml bacterial suspension (*P. multocida* strain 59A006) intraperitoneally. Each experiment has at least 3 non-medicated control groups including one infected with 0.1× challenge dose and two infected with 1× challenge dose; a 10× challenge data group may also be used. Generally, all mice in a given study can be challenged within 30–90 minutes, especially if a repeating syringe (such as a Cornwall® syringe) is used to administer the challenge. Thirty minutes after challenging has begun, the first compound treatment is given. It may be necessary for a second person to begin compound dosing if all of the animals have not been challenged at the end of 30 minutes. The routes of administration are subcutaneous or oral doses. Subcutaneous doses are administered into the loose skin in the back of the neck whereas oral doses are given by means of a feeding needle. In both cases, a volume of 0.2 ml is used per mouse. Compounds are administered 30 minutes, 4 hours, and 24 hours after challenge. A control compound of known efficacy administered by the same route is included in each test. Animals are observed daily, and the number of survivors in each group is recorded. The *P. multocida* model monitoring continues for 96 hours (four days) post challenge.

The PD_{50} is a calculated dose at which the compound tested protects 50% of a group of mice from mortality due to the bacterial infection that would be lethal in the absence of drug treatment.

The crystal forms of the present invention (hereinafter "the active compound(s)"), may be administered through oral, parenteral, topical, or rectal routes in the treatment or prevention of bacterial or protozoa infections. In general, the active compound is most desirably administered in dosages ranging from about 0.2 mg per kg body weight per day (mg/kg/day) to about 200 mg/kg/day in single or divided doses (i.e., from 1 to 4 doses per day), although variations will necessarily occur depending upon the species, weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of about 2 mg/kg/day to about 50 mg/kg/day is most desirably employed. Variations may nevertheless occur depending upon the species of mammal, fish or bird being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects, provided that such larger doses are first divided into several small doses for administration throughout the day.

The active compound may be administered alone or in combination with pharmaceutically acceptable carriers or diluents by the routes previously indicated, and such administration may be carried out in single or multiple doses. More particularly, the active compound may be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, sachets, powders for oral suspension, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the active compound is present in such dosage forms at concentration levels ranging from about 1.0% to about 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch (and preferably corn, potato or tapioca starch), alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatin capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the active compound may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For parenteral administration, solutions of the active compound in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH greater than 8) if

necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are suitable for intraarticular, intramuscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques will known to those skilled in the art.

Additionally, it is also possible to administer the active compound topically and this may be done by way of creams, jellies, gels, pastes, patches, ointments and the like, in accordance with standard pharmaceutical practice.

For administration to animals other than humans, such as cattle or domestic animals, the active compounds may be administered in the feed of the animals or orally as a drench composition.

The active compound may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

What is claimed is:

1. A crystalline form of azithromycin according to claim 20 wherein said azithromycin comprises more than 50% by weight of azithromycin sesquihydrate.

2. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 55% or more by weight of azithromycin sesquihydrate.

3. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 60% or more by weight azithromycin sesquihydrate.

4. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 65% or more by weight of azithromycin sesquihydrate.

5. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 70% or more by weight of azithromycin sesquihydrate.

6. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 75% or more by weight of azithromycin sesquihydrate.

7. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 80% or more by weight of azithromycin sesquihydrate.

8. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 85% or more by weight of azithromycin sesquihydrate.

9. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 90% or more by weight of azithromycin sesquihydrate.

10. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 91% or more by weight of azithromycin sesquihydrate.

11. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 92% or more by weight of azithromycin sesquihydrate.

12. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 93% or more by weight of azithromycin sesquihydrate.

13. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 94% or more by weight of azithromycin sesquihydrate.

14. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 95% or more by weight of azithromycin sesquihydrate.

15. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 96% or more by weight of azithromycin sesquihydrate.

16. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 97% or more by weight of azithromycin sesquihydrate.

17. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 98% or more by weight of azithromycin sesquihydrate.

18. A crystalline form of azithromycin according to claim 1, wherein said azithromycin comprises 99% or more by weight of azithromycin sesquihydrate.

19. A crystalline form of azithromycin according to claim 1 wherein said azithromycin comprises 99% or more by weight of azithromycin sesquihydrate.

20. The crystalling form of azithromycin according to claim 1 wherein said ^{13}C solid stat NMR spectrum further comprising a peak with chemical shift of about 10.4 ppm.

21. The crystalline form of azithromycin according to claim 20 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 9.9 ppm.

22. The crystalline form of azithromycin according to claim 21 wherein said ^{12}C solid state NMR spectrum further comprising a peak with chemical shift of about 9.3 ppm.

23. The crystalline form of azithromycin according to claim 22 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 7.6 ppm.

24. The crystalline form of azithromycin according to claim 23 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 6.5 ppm.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,977,243 B2
DATED : December 20, 2005
INVENTOR(S) : Li et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27, line 23 - Column 28, line 47,
Replace claims 1-24 with the following:

1. A crystalline form of azithromycin which is azithromycin sesquihydrate being characterized as having a ^{13}C solid state NMR spectrum comprising a plurality of peaks with at least one peak having a chemical shift of about 179.5 ppm.

2. A crystalline form of azithromycin according to claim 1 wherein said azithromycin comprises more than 50% by weight of azithromycin sesquihydrate.

3. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 55% or more by weight of azithromycin sesquihydrate.

4. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 60% or more by weight of azithromycin sesquihydrate.

5. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 65% or more by weight of azithromycin sesquihydrate.

6. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 70% or more by weight of azithromycin sesquihydrate.

7. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 75% or more by weight of azithromycin sesquihydrate.

8. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 80% or more by weight of azithromycin sesquihydrate.

9. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 85% or more by weight of azithromycin sesquihydrate.

10. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 90% or more by weight of azithromycin sesquihydrate.

11. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 91% or more by weight of azithromycin sesquihydrate.

12. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 92% or more by weight of azithromycin sesquihydrate.

13. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 93% or more by weight of azithromycin sesquihydrate.

14. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 94% or more by weight of azithromycin sesquihydrate.

15. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 95% or more by weight of azithromycin sesquihydrate.

16. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 96% or more by weight of azithromycin sesquihydrate.

17. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 97% or more by weight of azithromycin sesquihydrate.

18. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 98% or more by weight of azithromycin sesquihydrate.

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,977,243 B2
DATED : December 20, 2005
INVENTOR(S) : Li et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 27, line 23 - Column 28, line 47 (cont'd).

19. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 99% or more by weight of azithromycin sesquihydrate.

20. The crystalline form of azithromycin according to claim 1 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 10.4 ppm.

21. The crystalline form of azithromycin according to claim 20 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 9.9 ppm.

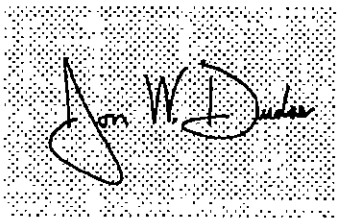
22. The crystalline form of azithromycin according to claim 21 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 9.3 ppm.

23. The crystalline form of azithromycin according to claim 22 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 7.8 ppm.

24. The crystalline form of azithromycin according to claim 23 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 6.5 ppm.

Signed and Sealed this

Seventh Day of February, 2006



JON W. DUDAS
Director of the United States Patent and Trademark Office

EXHIBIT H

We dedicate ourselves to humanity's quest for longer, healthier, happier lives through innovation in pharmaceutical, consumer and animal health products.

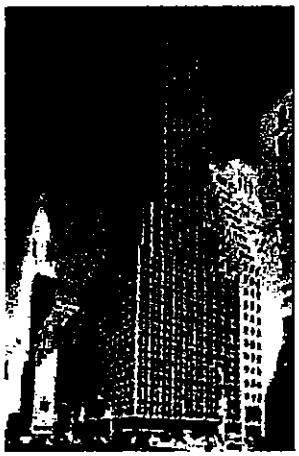
About Pfizer

Our Company

CEO:	Henry A. McKinnell, Ph.D.
Pfizer Locations:	**Corporate Headquarters:** New York, NY (USA) **Research & Development:** Groton and New London, Connecticut Sandwich, England Nagoya and Tokyo, Japan Amboise, France La Jolla, California Cambridge, Massachusetts Ann Arbor, Michigan **Consumer Health Care:** Morris Plains, New Jersey
Web Site Address:	http://www.pfizer.com
Stock Exchange Listings:	New York Stock Exchange (PFE) London (PFZ) Euronext Swiss
2005 Revenues:	$51.3 Billion
2005 Actual R&D Spending:	$7.4 Billion
Key Pfizer Pharmaceutical Products:	Aricept® (donepezil hydrochloride tablets)* Celebrex® (celecoxib) Diflucan® (fluconazole) Lipitor® (atorvastatin calcium) tablets Neurontin® (gabapentin) Norvasc® (amlodipine besylate) Viagra® (sildenafil citrate) tablets Xalatan® (latanoprost ophthalmic solution) Zithromax® (azithromycin) Zoloft® (sertraline HCl) Zyrtec® (certirizine HCl)

* Aricept® is a registered trademark of Eisai Co., Ltd.

Key Pfizer Consumer Health Care Products:	Benadryl® Cortizone® Desitin® e.p.t.® Listerine®	Lubriderm® Neosporin® Rolaids® Sudafed® Visine®
Key Pfizer Animal Health	Clavamox®/Synulox® Equimax®	



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Naxcel®/Excenel®
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Last Update: January 24, 2006

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Pfizer Inc is a pharmaceutical company committed to helping people improve their health by discovering and developing medicines.

EXHIBIT I

5/A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: **A. TRASK**

APPLICATION SERIAL NO.: **10/152,106** : Examiner: Not Yet Assigned

FILING DATE: **MAY 21, 2002** : Group Art Unit: 1623

TITLE: **CRYSTAL FORMS OF AZITHROMYCIN**

COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

Prior to examination on the merits, please amend the above-identified application as follows:

In the Specification:

On page 1, after the title, please insert the following: --This application claims the benefit of U.S. Provisional Application Serial No. 60/292,565, filed May 22, 2001; U.S. Provisional Application Serial No. 60/297,741, filed June 12, 2001; and U.S. Provisional Application Serial No. 60/343,041, filed December 21, 2001, the contents of the aforementioned provisional patent applications are hereby incorporated by reference in their entirety.--

The above amendment adds no new matter to this application. Applicants respectfully request its entry.

REMARKS

Applicants have amended the specification to include priority data as required pursuant 37 C.F.R. §1.78.

Applicants respectfully submit that no new matter is added to the present application.

Applicants have attached hereto a marked-up version of the changes made to the specification by the current amendment. The attached marked-up version is labeled "Version with Markings to Show Changes Made – Do Not Enter ". The marked-up version can be found following the signature page of this Amendment.

A favorable response is requested.

Respectfully submitted,

Date: September 23, 2002

Adrian G. Looney
Attorney for Applicants
Reg. No. 41,406

Pfizer Inc
Patent Department, 5th Floor
150 East 42nd Street
New York, NY 10017-5755
(212) 733-1038

Express Mail No. EL162816349 US

VERSION WITH MARKINGS TO SHOW CHANGES MADE – DO NOT ENTER

In the Specification

The following sentence containing the priority application data for the subject application has been added following the Title of the application on page 1 as follows: "This application claims the benefit of U.S. Provisional Application Serial No. 60/292,565, filed May 22, 2001; U.S. Provisional Application Serial No. 60/297,741, filed June 12, 2001; and U.S. Provisional Application Serial No. 60/343,041, filed December 21, 2001, the contents of the aforementioned provisional patent applications are hereby incorporated by reference in their entirety."

PATENT
Attorney Docket No. PC11714A US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the Patent of:	
Zheng J. Li *et al.*	
U.S. Patent No.: 6,977,243, issued December 20, 2005	Group Art Unit: 1623
Application No.: 10/152,106	
Filed: May 21, 2002	Examiner: Elli Peselev
Title: CRYSTAL FORMS OF AZITHROMYCIN	

Certificate of Correction Branch
Commissioner for Patents
P. O. Box 1450-
Alexandria, VA 22313-1450

REQUEST FOR EXPEDITED ISSUANCE OF A CERTIFICATE OF CORRECTION UNDER 37 C.F.R. §1.322 AND M.P.E.P. §1480.01

Dear Sir:

Patentee respectfully requests an expedited issuance of a Certificate of Correction under M.P.E.P §1480.01 to correct errors attributable to the United States Patent and Trademark Office, which are identified on Certificate of Correction form PTO/SB/44 enclosed herewith.

Patentee further requests that the Patent Office disregard the Certificate of Correction filed on January 6, 2006 which did not correct all of the errors in the patent.

No fee should be required for this request since the errors are due to the USPTO. Notably, the August 31, 2005 Index of Claims indicates that allowed claim 125 should be claim 1 in the issued patent and this claim was actually omitted in the issued patent. Moreover, the Index of Claims also indicates that allowed claims 36 – 53 should be claims 2-19 in the issued patent, not claims 1-18 as actually printed. Claims 20 – 24 in the issued patent (which

correspond to allowed claims 126-130) were numbered correctly. For your convenience, a copy of the August 31, 2005 Index of Claims, a copy of the issued claims as well as the Notice of Allowability and the pending claims before the issuance of the Notice of Allowance (i.e., from the Amendment filed on June 6, 2005) are enclosed.

The incorrect numbering of many of the claims in the patent has led to errors in the dependencies of many of the claims. These errors have also been corrected in the attached Certificate of Correction.

Patentee has also noticed that in the Examiner's amendment that was a part of the Notice of Allowability dated August 31, 2005, the Examiner's amendment to claim 125, line 3, appears to have added a second "with" to line 3 so that the language reads "with with at least one peak...". This is clearly an inadvertent error on the Examiner's part. Accordingly, Patentee has also corrected this obvious error in the attached Certificate of Correction.

Furthermore, the allowed claim 126 spells the words "crystalline" and "state" correctly although these words were misspelled in claim 20 of the issued patent as "crystalling" and "stat," respectively. Finally, in allowed claim 128, reference was made correctly to "^{13}C" solid state NMR although claim 22 of the patent refers incorrectly to "^{12}C" solid state NMR.

In view of the large number of errors in the claims of the patent, Patentee believes that that the easiest way to correct all of the errors is to submit a substitute set of claims for the patent. This substitute set of claims appears in the attached Certificate of Correction (form PTO/SB/44).

It is respectfully submitted that all of the errors that have been corrected in the substitute set of claims in the attached Certificate of Correction were made by the United States Patent and

Trademark Office. Accordingly, Patentee respectfully requests that a Certificate of Correction be issued on an expedited basis under M.P.E.P. § 1480.01.

No fee is believed to be necessary in connection with the filing of this Certificate of Correction. If, however, the Commissioner determines that any fee is due, the Commissioner is hereby authorized to charge any such fees, which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

Respectfully submitted,

Date: Jan. 18, 2006

Lance Liu

Lance Y. Liu
Attorney for Patentee
Reg. No. 45,379

Customer No. 28523
Pfizer Inc.
Patent Department, MS 8260-1611
Eastern Point Road
Groton, Connecticut 06340
(860) 686-1652

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.	:	6,977,243
APPLICATION NO.	:	10/152,108
ISSUE DATE	:	December 20, 2005
INVENTOR(S)	:	Zheng J. Li and Andrew V. Trask

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Please replace claims 1 – 24 of the patent with the following set of corrected claims:

1. A crystalline form of azithromycin which is azithromycin sesquihydrate being characterized as having a ^{13}C solid state NMR spectrum comprising a plurality of peaks with at least one peak having a chemical shift of about 179.5 ppm.

2. A crystalline form of azithromycin according to claim 1 wherein said azithromycin comprises more than 50% by weight of azithromycin.sesquihydrate.

3. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 55% or more by weight of azithromycin sesquihydrate.

4. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 60% or more by weight of azithromycin sesquihydrate.

5. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 65% or more by weight of azithromycin sesquihydrate.

6. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 70% or more by weight of azithromycin sesquihydrate.

7. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 75% or more by weight of azithromycin sesquihydrate.

8. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 80% or more by weight of azithromycin sesquihydrate.

9. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 85% or more by weight of azithromycin sesquihydrate.

10. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 90% or more by weight of azithromycin sesquihydrate.

11. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 91% or more by weight of azithromycin sesquihydrate.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Lance Y. Liu,
Pfizer, Inc., Patent Department, MS 8260-1611
Eastern Point Road, Groton, Connecticut 06340

PTO/SB/44 (04-05)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.
(Also Form PTO-1050)

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,977,243

APPLICATION NO. : 10/152,106

ISSUE DATE : December 20, 2005

INVENTOR(S) : Zheng J. Li and Andrew V. Trask

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

(corrected set of claims continued from page 1)

12. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 92% or more by weight of azithromycin sesquihydrate.

13. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 93% or more by weight of azithromycin sesquihydrate.

14. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 94% or more by weight of azithromycin sesquihydrate.

15. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 95% or more by weight of azithromycin sesquihydrate.

16. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 96% or more by weight of azithromycin sesquihydrate.

17. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 97% or more by weight of azithromycin sesquihydrate.

18. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 98% or more by weight of azithromycin sesquihydrate.

19. A crystalline form of azithromycin according to claim 2, wherein said azithromycin comprises 99% or more by weight of azithromycin sesquihydrate.

20. The crystalline form of azithromycin according to claim 1 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 10.4 ppm.

21. The crystalline form of azithromycin according to claim 20 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 9.9 ppm.

22. The crystalline form of azithromycin according to claim 21 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 9.3 ppm.

23. The crystalline form of azithromycin according to claim 22 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 7.6 ppm.

24. The crystalline form of azithromycin according to claim 23 wherein said ^{13}C solid state NMR spectrum further comprising a peak with chemical shift of about 6.5 ppm.

MAILING ADDRESS OF SENDER (Please do not use customer number below):
Lance Y. Liu,
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Eastern Point Road, Groton, Connecticut 06340